The American Journal of Medicine

January 1947

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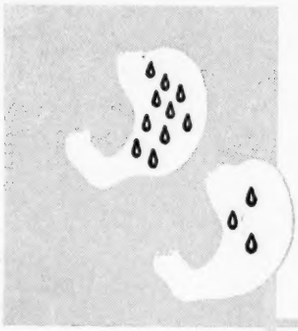

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1. Meyer, Soler, and Neuwelt: Arch. Int. Med. 65:171, 1940

2. Kapelowitz: J. Missouri M. A.: 38:55, 1941

3. Rivers: Proc. Staff Meet., Mayo Clin. 13:87, 1938

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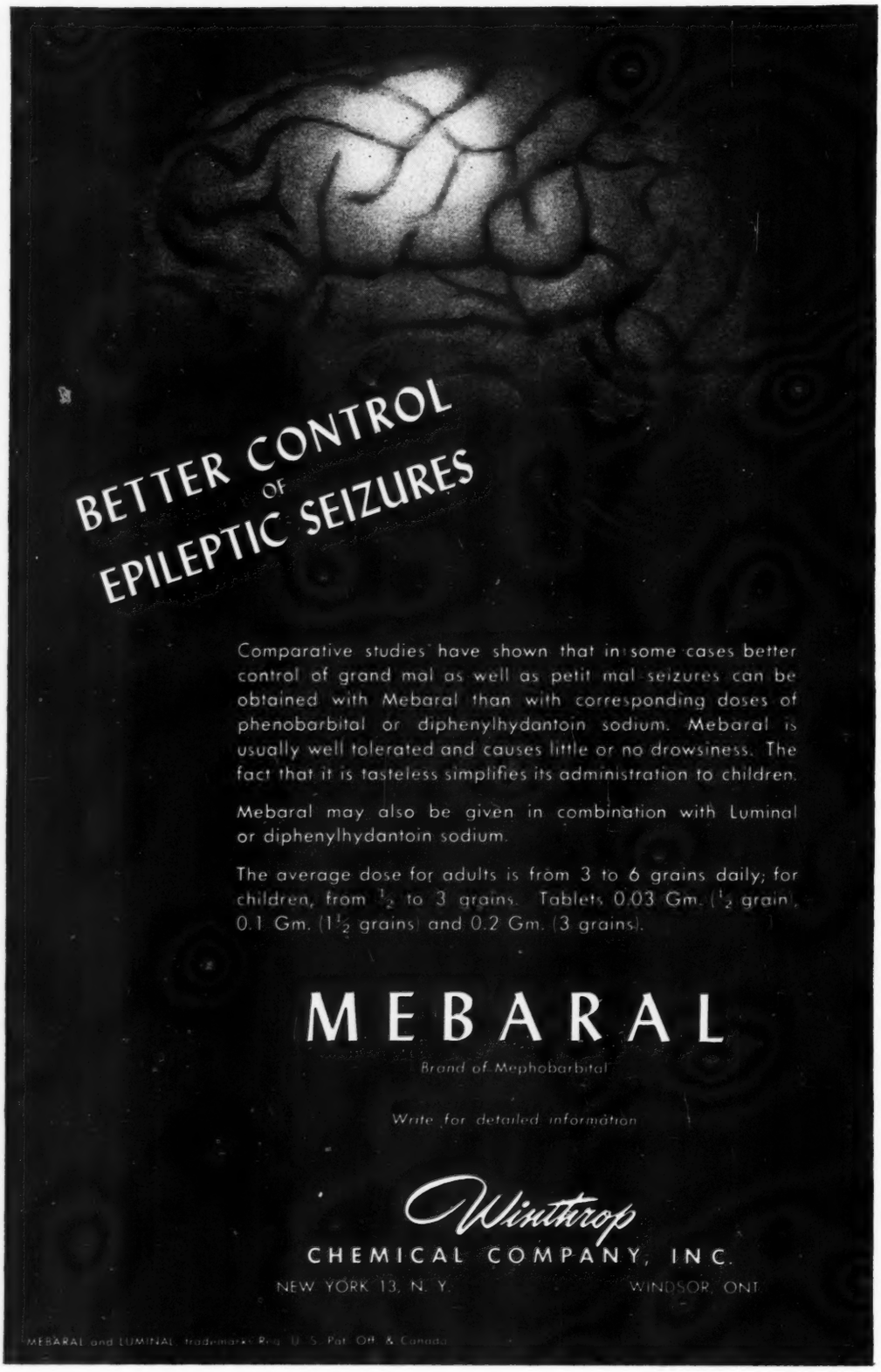
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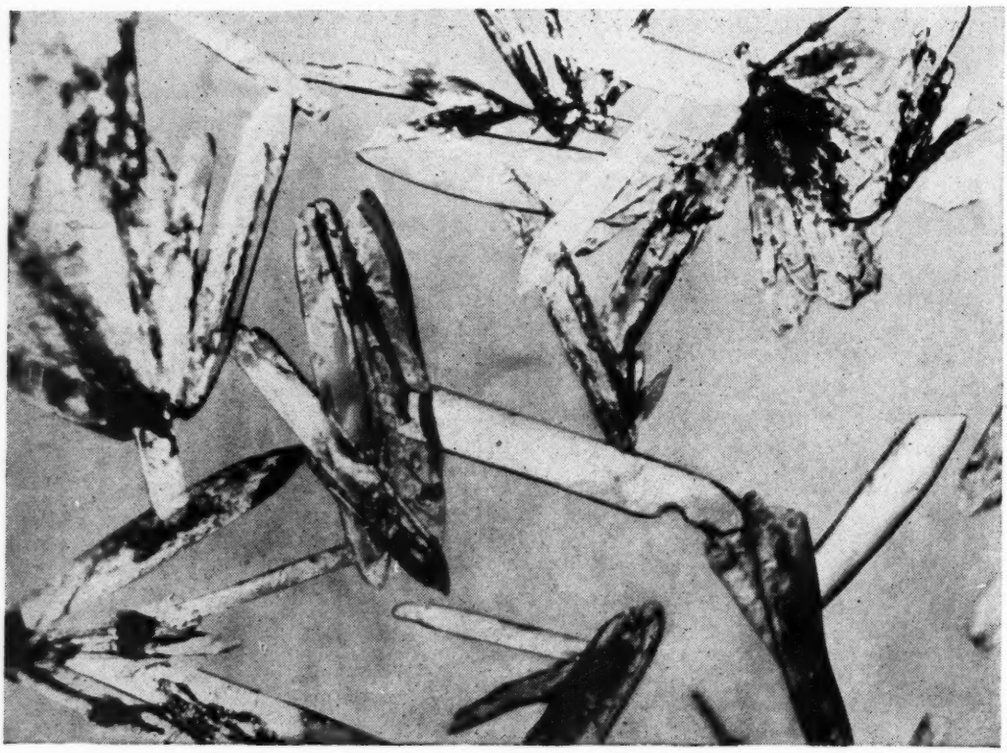

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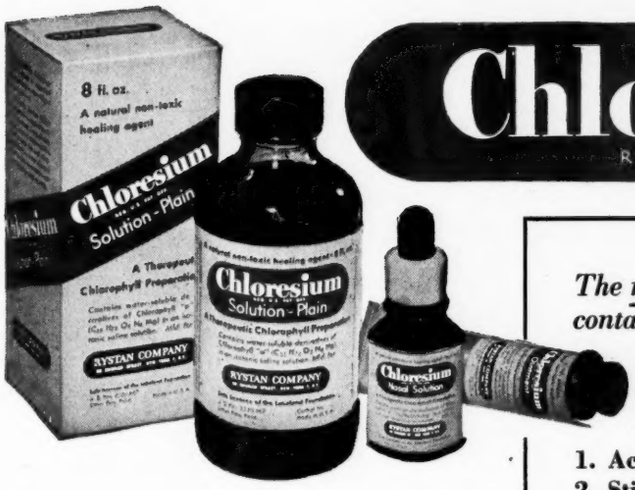

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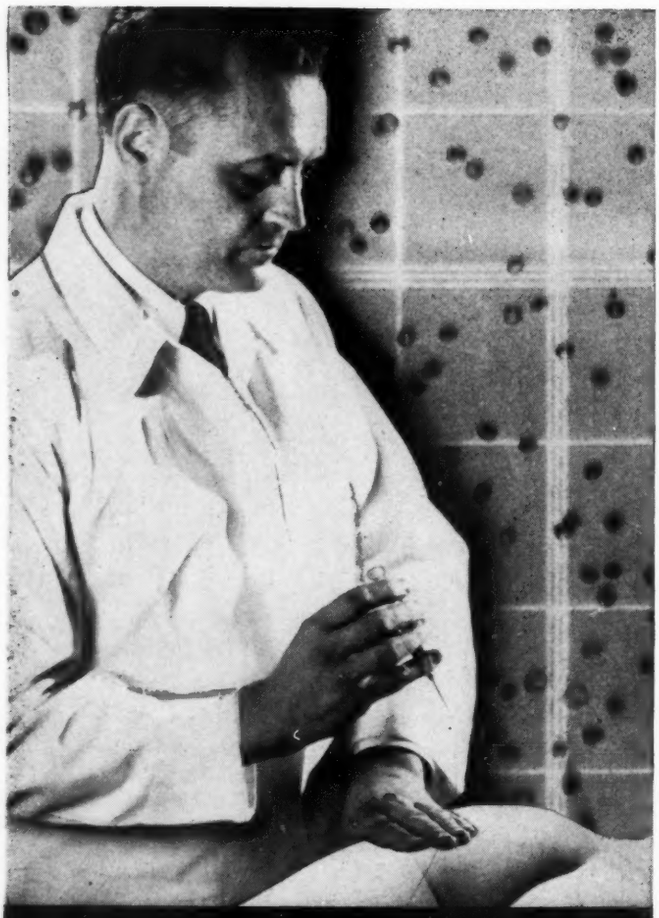

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1. Jordan, S. M., Surg. Clin. North America *21*:665, 1941. 2. Rehfuss, M. E., Clinics *3*.480, 1944. 3. Alvarez, W. C., J.A.M.A. *125*:903, 1944.

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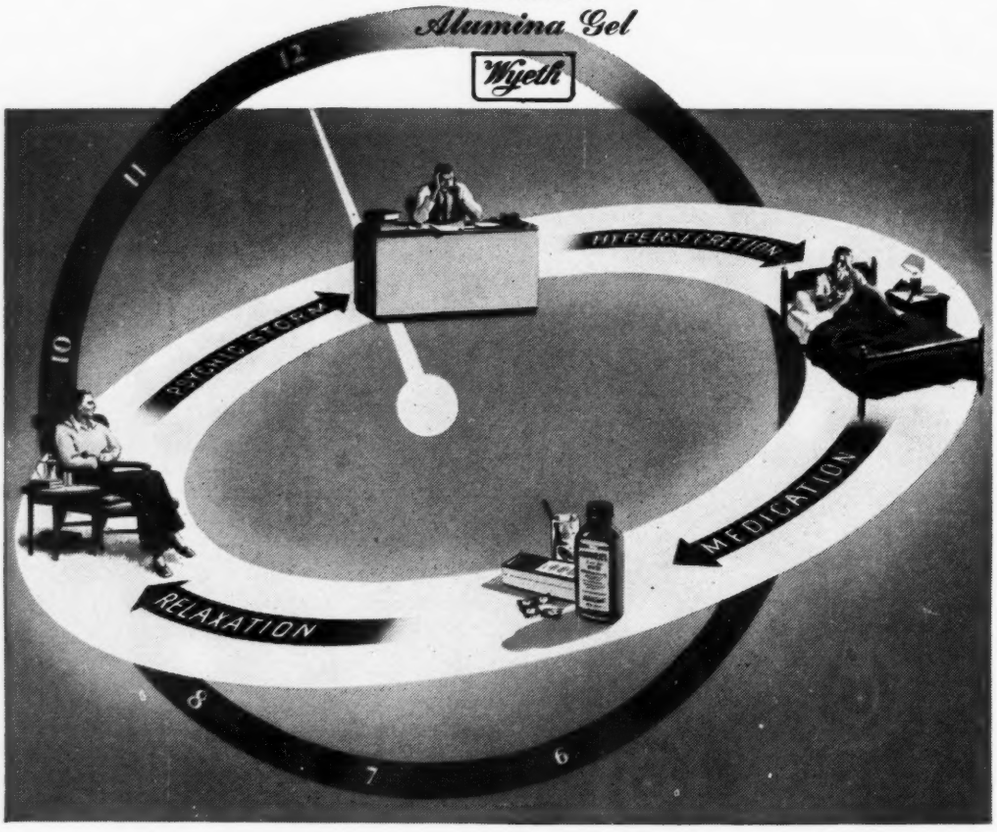

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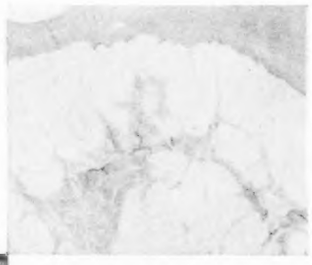

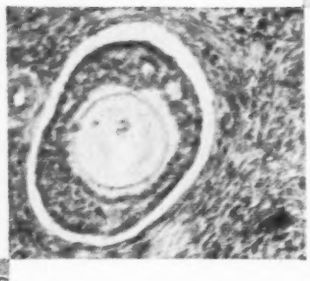

Color photomicrograph of section of ovary showing corpus luteum.

Color photomicrograph of section of ovary showing graafian follicle.

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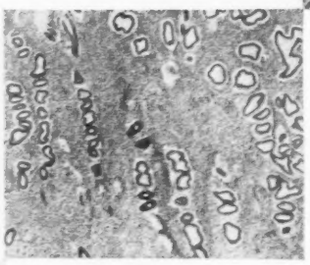
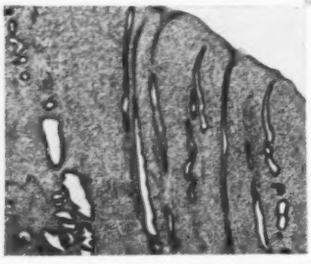


Color photomicrograph of endometrium during secretory stage.



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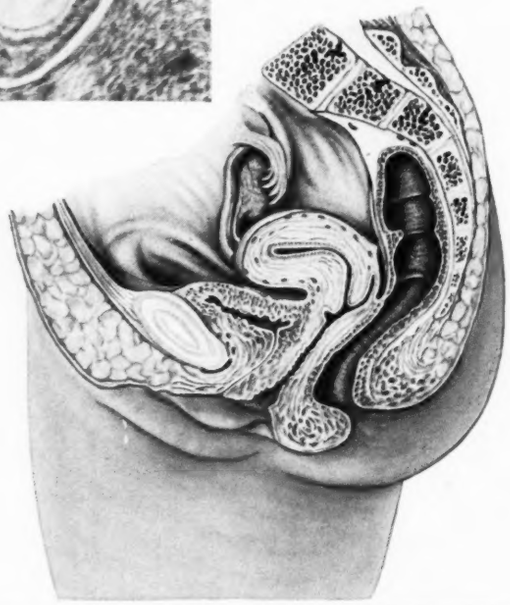

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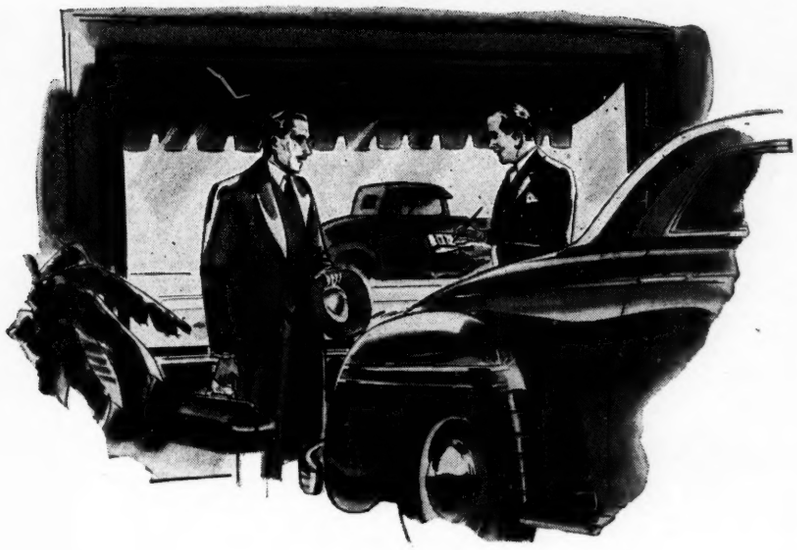

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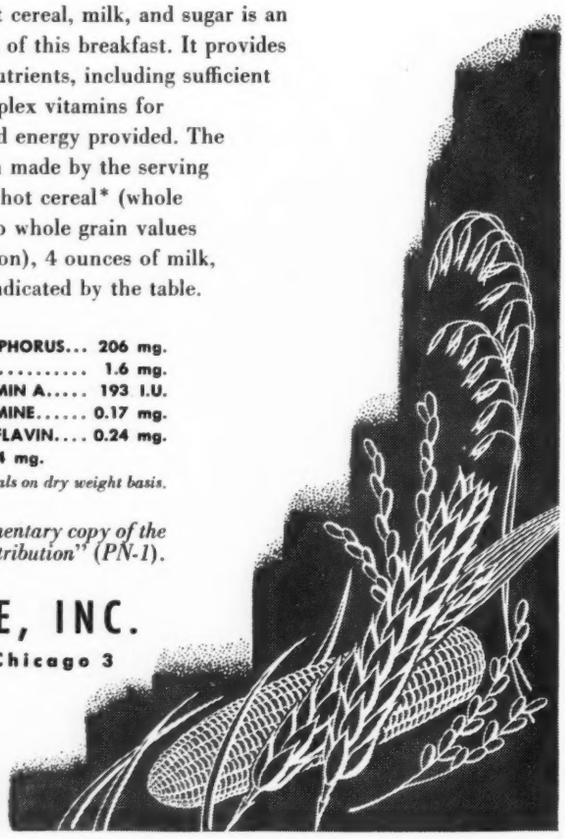

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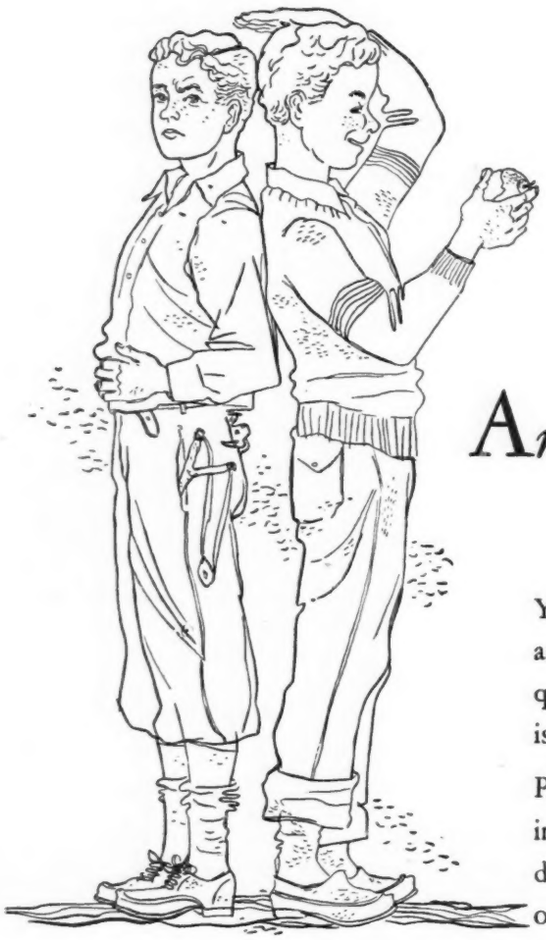

An answer that raises a question

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The American Journal of Medicine

VOL. II JANUARY, 1947 No. 1

Penicillin Therapy of Scarlet Fever and the Streptococcus Carrier*

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EAST ORANGE, NEW JERSEY ROCHESTER, MINNESOTA

SINCE its development, penicillin has been widely used as a therapeutic agent in numerous diseases. Its usefulness is now generally considered to be limited to diseases produced by the gram-positive organisms, Neisseria, spirochetes, fusiforms of Vincent, Streptobacillus moniliformis and a few others. It has been found to be highly effective against the group A hemolytic streptococci. Cases of its effectiveness in streptococcal infections after failure with sulfonamides have been described,[6] and comparisons of penicillin and the sulfonamides have been made on numerous occasions.[1,8,11] No direct study of the effect of penicillin on group A hemolytic streptococci known to be specifically resistant to the sulfonamides, however, has yet appeared.[2]

Attempts to evaluate proper and adequate doses for the various diseases susceptible to penicillin therapy have been made.[13] Plummer and his associates studied the specific effect of intramuscular administration of penicillin in hemolytic streptococcal pharyngitis and tonsillitis. They found a temporary suppression of positive cultures using 15,000 units every four hours but noted that relapses of both cultures and symptoms occurred if administration of the drug was discontinued in less than six days. They also found that sulfadiazine reduced the number of organisms in nose and throat cultures but only during the period of exposure to the drug. This effect of sulfadiazine has also been noted elsewhere.[15]

Meads and his associates[10] presented a study of the effect of penicillin treatment in scarlet fever in children. They likewise studied the effect of this drug on the carrier state, noting a depression of the number of organisms obtained from the nose and throat, as demonstrated culturally. A reduction of the number of hemolytic streptococci was also observed under sulfonamide therapy, as had also been described by Julianelle and Seigel.[7] These authors also studied the effect of penicillin spray on streptococci in the nose and throat and were unable to obtain a significant decrease in the organisms present.

Hamburger and his associates[4,5] recently studied the carrier problem and came to the conclusion that a certain percentage of persons are "dangerous," in that they carry streptococci in their noses for months. Positive nasal cultures were found to be a more significant index of the carrier state than throat cultures. These findings are essentially in accord with those of DeLamater

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and others[2] who found persistent positive cultures to be associated with definite nasopharyngeal pathologic changes. Numerous carriers and cross infections due to carriers who had persistent nasopharyngeal disease were noted.

The present paper will deal further with the carrier problem and the effect of penicillin on the carrier state.

SOURCE OF MATERIAL

DeLamater and his co-workers reported the occurrence and development of an epidemic of streptococcal disease in an army camp during the winter of 1944 and 1945. This epidemic was produced by a single strain of group A, type 17 (Lancefield) hemolytic streptococcus[16] which was specifically resistant to the sulfonamides. The epidemic developed in the face of sulfadiazine prophylaxis. Cases derived from this epidemic afforded an opportunity for a large scale study of the therapeutic effect of sulfadiazine and penicillin, as well as an opportunity for an evaluation of their effects on the carrier state in the respiratory diseases caused by hemolytic streptococci. It may be pointed out further that this epidemic, because of its causation by a single specific type of streptococcus, offered a unique opportunity to observe and study not only the range of variation of the disease produced by a single strain of a single type of streptococcus in a fairly uniform population, but also the effects of therapeutic agents in disease caused by such a single strain. Variations in the susceptibility of different strains and types of streptococci to a given therapeutic agent were automatically eliminated.

The epidemic occurred in young men of military age, and primarily in those new to military life. Table 1 demonstrates this. In 271 cases so analyzed in which type 17 streptococcus was the causative organism, 80 per cent had less than three months' service and 73 per cent were eighteen years of age. The population infected, therefore, was as uniform as could be expected.

TABLE 1
LENGTH OF SERVICE AND AGE OF PATIENTS

Length of service, months	Cases	Age, years	Cases
0–1	109	18	197
1–2	87	19	27
2–3	20	20	5
3–6	17	21–25	19
More than 6	38	26–30	14
		More than 30	9

Potential patients were all seen in sick call. All those who had sufficiently severe clinical manifestations of fever or rash, or a combination of these, were admitted directly to the hospital. As soon as possible, usually within six hours after admission to the hospital, throat cultures were obtained from all patients who had respiratory disease. During the latter part of the epidemic, isolation was strictly adhered to in all cases of respiratory disease. Patients who obviously had scarlet fever on admission were sent directly to wards set aside for them. Patients who had tonsillitis and nasopharyngitis were isolated as strictly as possible in the wards to which they were first assigned. Patients who had pneumonia were isolated.

Methods. All bacteriologic technics were the same as those described in a previous report.[2,3,17] Penicillin was made up by the usual methods for intramuscular injection.

Figure 1 demonstrates the pattern of the epidemic in total cases per week. This graph further shows the breakdown of the total cases into the four most common clinical conditions encountered. It is particularly interesting to note the distribution of the diseases. Scarlet fever was the most important single disease and reflects the epidemic pattern most closely. The differentiation of

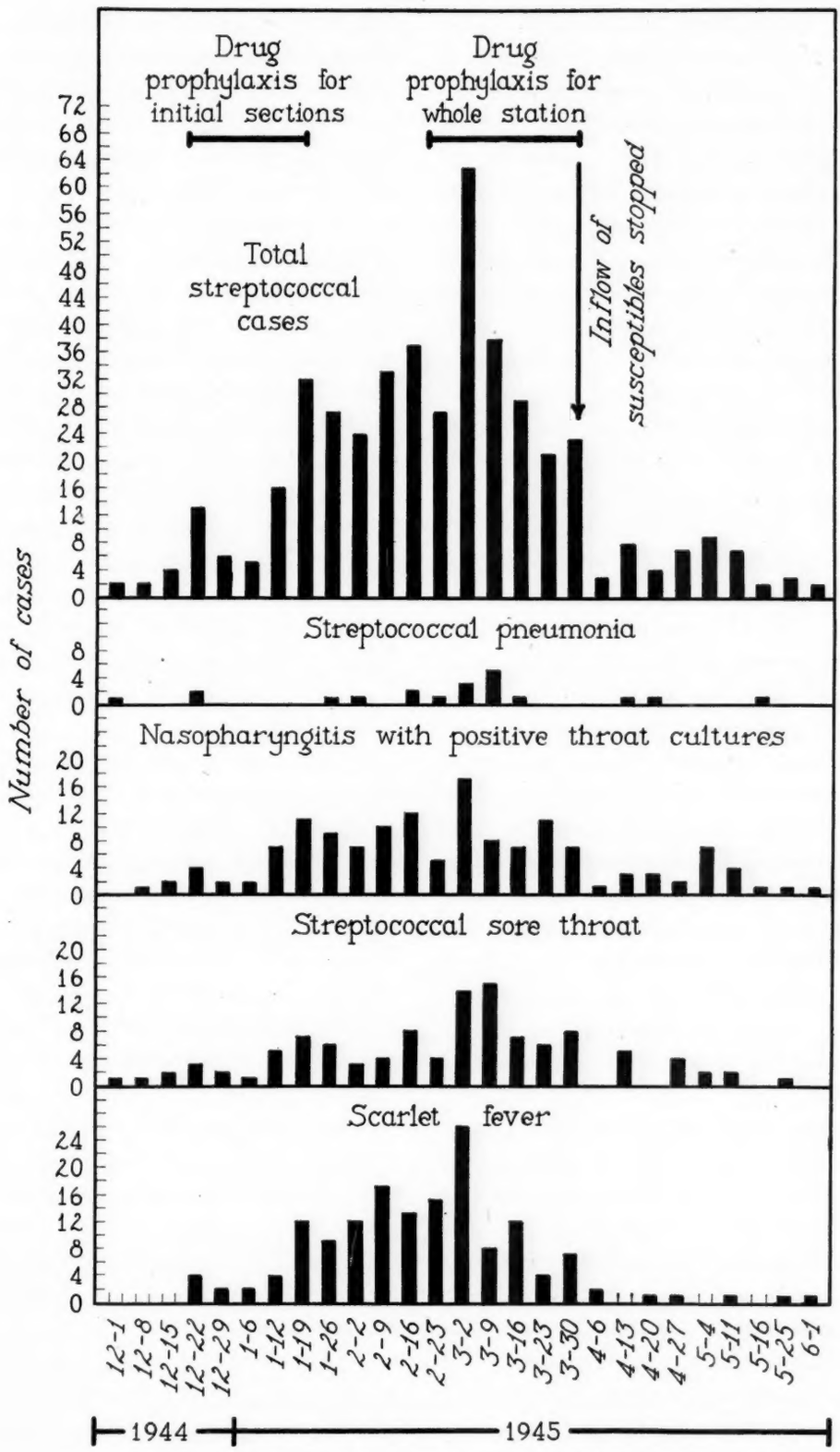

FIG. 1. Distribution of group A, type 17, streptococcal infections by weeks.

true streptococcal sore throat and nasopharyngitis with positive throat culture was made on clinical grounds. The patients who had nasopharyngitis without positive cultures differed in no way, either clinically or in the course of the disease, from those who had positive cultures, except that those who had positive cultures presented numerous problems of carrier control. We were never able to decide whether the positive cultures were incidental and clinically not significant, or whether this condition represented a very mild streptococcal disease which simulated a common cold (nasopharyngitis).

CLINICAL DESCRIPTION OF DISEASES ENCOUNTERED

Nasopharyngitis with Positive Cultures. This disease was mild. The men were acutely ill for twenty-four to forty-eight hours with temperatures ranging between 100° and 103°F. They suffered from acute malaise, headache, rhinitis and cough. The throat was injected but not follicular. After twenty-four hours of rest in bed and adequate intake of fluid, the fever and other symptoms subsided and the men were ready for full duty in three to five days. There were 111 such cases. They differed from the usual nasopharyngitis only in the occurrence of positive throat cultures for type 17 streptococcus.

Streptococcal Sore Throat. One hundred fourteen cases of streptococcal sore throat were observed. In these cases soreness of the throat developed with difficulty in swallowing. Temperatures of 102° to 104°F. (or higher) were present on admission and persisted for two to four days. The throat presented generalized erythema, with exudate on the tonsils or tonsillar pillars (or both) and follicles on the lymphoid tissue in the posterior pharynx. Treatment consisted of saline gargle, with the use of sulfadiazine in the early phase of the epidemic. Later penicillin was used in the more serious conditions. Treatment of the complications followed that described under scarlet fever.

Scarlet Fever. During the winter of 1944 and 1945, 155 cases of scarlet fever due to group A, type 17, beta-hemolytic streptococci were studied.

Clinically the disease varied in intensity during this period. At the onset of the epidemic the disease was severe. It became milder toward the middle of the epidemic period but again became severe during the latter part. The rash was intense and appeared two to three days after the onset of sore throat. Sore throat was intense with marked dysphagia. The throats presented generalized, marked erythema, with exudate on the tonsils and tonsillar pillars. Edema of the pharynx was common. There was moderate toxicity with headache, weakness and vomiting with initial chills. In a tenth of the cases there was a hemorrhagic rash.

During the early stages of the epidemic, Schultz-Charlton tests done with commercial antiserums gave negative results. In ten later cases the test was performed utilizing 0.2 cc. of convalescent serum from a patient who had recovered from type 17 scarlet fever. There was excellent blanching of the rash 2 cm. around the site of injection. Commercial scarlet fever antitoxin used in the same manner on the same patient gave negative results.

The patients in this series of scarlet fever were divided into three groups, according to the form of treatment which they received: those treated with penicillin, those treated with sulfadiazine and those treated symptomatically. These will be considered in detail later.

Rheumatic Fever. In only one case of group A, type 17 streptococcal infection did rheumatic fever develop. Approximately one week after the onset of severe hemorrhagic scarlet fever, aching and pain developed in all of the patient's joints. While

there was no swelling, redness or heat in any of the joints the patient was closely observed for rheumatic fever even though the early clinical picture was more that of infectious arthritis. The patient improved symptomatically when salicylates were administered, but repeated electrocardiograms and examinations of his heart failed to reveal any evidence of carditis. The sedimentation rate remained elevated for approximately seven weeks, and during the eighth week an aortic diastolic murmur was heard for the first time. Definite aortic insufficiency then rapidly developed and the diagnosis of rheumatic fever was apparent. The patient's antistreptolysin titer curve was typical of rheumatic fever.

In spite of the increased incidence of streptococcal infections there were fewer cases of rheumatic fever at Keesler Field during the winter and spring of 1944 and 1945 than had occurred in previous years. There seemed to be no relationship between the incidence of streptococcal infection (at least type 17) and the incidence of rheumatic fever. This is illustrated in Table II

TABLE II
CASES OF SCARLET FEVER AND OF RHEUMATIC FEVER AT KEESLER FIELD

November–May	Scarlet Fever	Rheumatic Fever
1942–43	35	12
1943–44	19	10
1944–45	166	5

in which the total number of cases of scarlet fever associated with all types of streptococci is compared with the number of cases of rheumatic fever developing at Keesler Field during three years. This raises the question of whether the causation of rheumatic fever may be a specific character of a given strain or type of streptococcus. Keogh and Kelsey[9] expressed the belief that the disease pattern produced by a given strain of streptococcus (as demonstrated in Figure 1) may be a rather specific character of the race, strain, or type under consideration.

Streptococcal Pneumonia. There were twenty cases in which group A, type 17, hemolytic streptococcal pneumonia developed. Seven of these were secondary to scarlet fever and were relatively milder than the primary streptococcal pneumonias caused by the same strain. Four of the patients had a massive pleural effusion and three others had pleurisy. All of these patients were treated with penicillin and made a satisfactory recovery except for one patient who is discussed under the heading "acute nephritis."

The cases of severe primary streptococcal pneumonia were characterized by a sudden onset with a temperature up to 105° and 106°F. The sputum was scanty, usually mucoid or mucopurulent, rarely blood-tinged and never frankly bloody. The leukocyte count was high, usually 20,000 or more per c.mm. of blood. With penicillin treatment the temperature fell over a three- or four-day period by lysis.

When an effusion developed it came early in the disease, so early in fact that in some instances it masked the underlying pneumonitis even on the first physical examination. The policy in these cases was to tap the thorax early and to instill penicillin into the pleural cavity. The fluid obtained was cloudy and amber colored and did not clot on standing. A direct smear failed to show the organisms, and, while they grew on culture, they did so only on blood agar plates in the presence of carbon dioxide. Several of these organisms had a distinctly greenish hue but were easily typed by the usual methods. In subsequent culture they lost their greenish coloration and grew readily aerobically. Instillation of 35,000 to 40,000 units of penicillin so sterilized the pleural fluid that positive cultures could not thereafter be obtained. These chests were

TABLE III

COMPLICATIONS OF VARIOUS DISEASES

Diseases	Complications								Total Cases	Total Complications	Per Cent of Cases with Complications
	Cervical Adenitis	Otitis Media	Bacterial Pneumonia	Sinusitis	Pleurisy	Tonsillitis (recrudescent)	Peritonsillar Abscess	Other			
Scarlet fever	43	19	7	12	3	2	3	13	155	102	65.8
Streptococcal sore throat	12	8	2	6	0	0	9	7	114	44	38.6
Nasopharyngitis	1	6	12	1	1	2	0	4	111	27	24.3
Streptococcal pneumonia	2	2	0	2	3	0	0	1	20	10	50.0
Primary atypical pneumonia	0	1	0	1	0	2	0	1	21	5	23.8
Miscellaneous streptococcal diseases	2	0	0	0	0	0	0	2	18	4	22.2

tapped either daily or every other day with the instillation of penicillin after each tap. Three or four taps usually sufficed and in no case did empyema develop.

Acute Nephritis. A thirty-seven year old soldier who had two years' service entered the hospital for sore throat of two days' duration. Examination gave negative results except for a diffusely congested pharynx and purulent postnasal discharge consistent with nasopharyngitis and sinusitis. Throat culture on admission revealed group A, type 17, hemolytic streptococci. Urine on admission showed albumin 1+. The temperature on admission of 103.4°F. dropped to normal in five days under symptomatic treatment but there was thereafter a low grade fever with a temperature of 100°F. On the thirteenth day in the hospital the urine showed albumin 4+ and numerous erythrocytes and leukocytes. Blood pressure was 145 mm. of mercury systolic and 90 diastolic. Edema of the eyelids appeared. The urine continued to show albumin and cellular elements. The concentration of urea nitrogen rose from 16.6 to 66 mg. per 100 cc. of blood. Moist râles were heard over the bases of both lungs and these, combined with tachycardia, falling blood pressure and temperature of 99°F. indicated myocardial failure. Anoxia developed and death occurred twenty days after admission.

Necropsy revealed subacute glomerulonephritis with interstitial bronchopneumonia of both bases due to group A, type 17, beta hemolytic streptococci. There was plugging of the bronchi, with atelectasis of the lower lobe of the right lung, and fibrous pleurisy of the lower lobe of the right lung. This was the only death which occurred at Keesler Field for which this organism was directly responsible. However, deaths occurred at other stations to which this strain of streptococcus was transmitted via troop shipments.[12,14,17]

COMPARISON OF COMPLICATION RATES IN THE DISEASES CAUSED BY GROUP A, TYPE 17, STREPTOCOCCI

A comparison of the complication rates of the diseases occurring in this epidemic is interesting. Table III shows the occurrence

of complications in the diseases observed. The percentage of complications gives an index of the relative severity of the three predominant diseases. As expected, more complications occurred in scarlet fever than in simple streptococcal sore throat, and relatively more complications in the latter disease than in nasopharyngitis with positive throat cultures. Streptococcal pneumonia lies halfway between scarlet fever and streptococcal sore throat in the incidence of complications. Interestingly, primary atypical pneumonia, which is of virus origin, parallels nasopharyngitis with positive cultures in incidence of complications.

Of all complications cervical adenitis was the most common, otitis media next and sinusitis third. Why there was such a high incidence of streptococcal pneumonia as a complication in the nasopharyngitis group was not apparent, but it seems likely that it was related to the difficulties encountered in the management of these patients, who considered themselves well by the second day of hospitalization.

THERAPEUTIC STUDIES IN SCARLET FEVER

The cases of scarlet fever were divided into three groups: (1) those in which treatment was symptomatic; (2) those in which sulfadiazine was used, and (3) those in which penicillin was used.

Symptomatic Treatment. A total of fifty-one patients who had group A, type 17, beta-hemolytic streptococcal scarlet fever were treated symptomatically. Basic treatment consisted of rest in bed for ten days, minimal fluid intake of 3,000 cc., zinc chloride astringent gargle for sore throat and acetylsalicylic acid for discomfort. In the initial cases in this group the disease was generally mild. Later cases were used as controls of the penicillin treated groups inasmuch as it was believed that penicillin could be used effectively for any complications that might arise. Despite the mildness of the disease in the untreated group, the rash persisted for an average of six days as contrasted with four days in the group treated with penicillin. Fever persisted for five days in the untreated group in contrast to three days for the group treated with penicillin. The group treated with sulfadiazine fell midway between the two other groups, the rash lasting for five days and fever for four days.

The complications of the group that received symptomatic treatment are indicated in Table IV. They serve as a base line for the effectiveness of the other forms of treatment. Complications were treated with penicillin with excellent results. In cases of otitis media the tympanic membrane was incised at the onset. No permanent perforation or mastoiditis resulted.

Table IV shows a comparison of the complication rates of the three groups of cases. As expected, the symptomatically treated group had the highest percentage of complications (78 per cent). The higher percentage of complications which occurred in the group treated with sulfadiazine (70 per cent) as compared with the lower rate occurring in those treated with penicillin (55 per cent) is as expected. However, these results also suggest that sulfadiazine may have some effect in the body against an organism which is strongly resistant in the test tube and which otherwise clinically appears to be unaffected by the drug. The rate of complications in the sulfadiazine treated group lies between the other two. It should be emphasized that the group treated with penicillin includes all cases, no matter how or in what dosage the drug was given.

Table V shows nineteen of the cases in which symptomatic treatment was used, with a record of the throat cultures, indicated by the type of streptococcus isolated, taken daily or every three or four days. Unfortunately all cases in this group could not be

TABLE IV

COMPARISON OF COMPLICATION RATES IN THE THREE MODES OF TREATMENT USED

	Total Cases	Complication													Total Complications	Per cent Complications
		Cervical Adenitis	Otitis Media	Paranasal Sinusitis	Peritonsillar Abscess	Secondary Tonsillitis	Secondary Bacterial Pneumonia	Pleural Effusion	Erythema Multiforme	Rheumatic Fever	Nephritis	Septicemia	Sulfadiazine Reactions	Other		
Total cases of scarlet fever..	155	43	19	12	3	2	7	3	1	1	0	0	4	7	102	65
Symptomatic treatment.....	51	16	11	5	2	0	1	1	1	0	0	0	0	3	40	78
Sulfadiazine treatment.....	30	8	2	2	1	0	1	1	0	0	0	0	4	2	21	70
Penicillin treatment.....	74	19	6	5	0	2	6	1	0	1	0	0	0	1	41	55

followed culturally. The complication, day of complication and complicating type are also shown. The persistence of positive throat cultures for as long as thirty-five days is visualized. The carrier problem that this raises will be discussed more fully presently.

This group of nineteen cases in which cultures were taken does not reflect the total complication rate for the group. (Table IV.)

Sulfadiazine Treatment. There were thirty cases in which scarlet fever was treated with sulfadiazine. This group comprises the cases of scarlet fever that occurred between January 26, 1945, and February 15, 1945, before sulfadiazine prophylaxis was instituted for all personnel of the station. Generally this group represented milder cases than the initial group treated with penicillin. It was decided to treat this group of patients with sulfadiazine since penicillin was available only for cases of severe disease. These patients were treated with 4 Gm. of sulfadiazine daily for eight days. In general, the temperature dropped to normal in four to five days, with disappearance of the rash in five days. The throat continued symptomatically sore for three days in contrast to the group treated with penicillin in which there was symptomatic improvement in twelve to twenty-four hours.

The complications in the group treated with sulfadiazine are shown in Table IV. The rates are significantly higher than in the group treated with penicillin when one considers that in these cases the disease was milder than in the cases in which penicillin was used. In cases of otitis media the tympanic membrane was incised and the patient was given penicillin for three to seven days. Complicating paranasal sinusitis was likewise treated with penicillin. One case of secondary pneumonia occurred which was also treated with penicillin.

It is noteworthy that the rate of occurrence of otitis media is much smaller in the group treated with sulfadiazine than in the group treated symptomatically. Although in the group treated with sulfadiazine the disease was generally milder, the difference may not be significant. However, it suggests at least partial inhibition of the growth of the organisms by the large doses used and suggests that there is a difference in drug sensitivity *in vivo*. However, daily throat cul-

tures of the patients treated with sulfadiazine showed persistence of the hemolytic streptococci in large numbers in the nasopharynx of these patients.

Table VI shows a group of seven of the patients treated with sulfadiazine who were followed by daily culture. The presence of the streptococcus is indicated by the type isolated. The complication, the day the complication occurred and the complicating type, if definitely known, are also shown. The total dosage of the drug is also given. Here also the persistence of positive throat cultures is apparent. It is evident that sulfadiazine in the usual therapeutic dosage did not affect the carrier state.

The complication rate for the patients of Table VI was 42.8 per cent. The total com-

TABLE V

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED SYMPTOMATICALLY (NO SPECIFIC THERAPY)

Case	Day in Hospital																																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
1	..	17	..	..	17	..	..	..	17	..	..	0																							
2	..	17	..	..	17	..	..	..	17	..	0																								
3	17	17	..	..	17	..	..	..	17	..	17																								
4	..	..	..	17	..	..	..	17	..	..	0																								
5	17	..	..	..	..	..	..	..	..	..	17	..	..	17																						
6	..	17	..	..	..	17	..	..	17	..	..	..	17	..	..	0																				
7	..	17	..	..	..	17	..	..	17	..	..	..	17	..	..	0	..	..	..	17																
8	17	..	..	17	..	..	..	17	..	..	+	..	..	..	+	..	..	0	..	..	..	17														
9	17	..	..	17	..	..	0	..	..	..	17	..	..	17	..	..	..	0	..	17																
10	17	..	17	..	..	17	..	..	..	17	..	..	17	..	..	..	17	..	..	0																
11	..	..	..	17	..	17	..	..	..	17	..	..	17	..	..	..	19	..	..	17																
12	..	17	..	..	..	..	17	..	..	17	..	..	..	17	..	..	0	..	..	..	17															
13	..	17	..	..	17	..	..	..	..	17	..	..	..	17	..	..	0	..	..	..	17															
14	..	17	..	..	17	17	17	17	17	17	0	G	17	17	17	17	17	17	17	NT	0															
15	..	17	..	17	17	NT	..	..	17	..	17	..	..	0	0	17	17	17	0	..	..	..	17	..	..	..	+	..	..	+						
16	..	17	..	..	..	..	..	17	..	..	C	..	..	..	17	..	..	17	..	..	..	17	..	..	17											
17	..	17	..	..	..	..	..	..	17	..	..	0	..	..	..	..	..	..	17	..	17	..	0	..	..	17	..	..	..	17	..	..	C	..	17	
18	..	+	17	..	..	..	17	..	..	+	..	..	..	17	..	..	17	..	..	..	17	..	17	17	17	17	17	17	C	17	17					
19	..	17	..	..	..	..	..	..	..	..	..	17	17		17	17	17	17	17	17	0	17	17	17	17	0	17	17	17	17	17	17	17	0	17

N.B.: NT = No type; C = Group C streptococci; G = Group C streptococci; + = Culture lost before grouping or typing was done.

TABLE V—(*Continued*)
RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED SYMPTOMATICALLY (NO SPECIFIC THERAPY)

Case	Complication	Day of Complication	Initial Type	Complicating Type
1	.....	.....	17	
2	.....	.....	17	
3	Cervical adenitis	3	17	17
4	.....	.....	17	
5	.....	.....	17	
6	.....	.....	17	
7	.....	.....	17	
8	Cervical adenitis	5 and 11	17	17 and 17?
9	.....	.....	17	
10	.....	.....	17	
11	Cervical adenitis	4	17	17
12	Cervical adenitis	7	17	17
13	.....	.....	17	
14	.....	.....	17	
15	.....	.....	17	
16	Cervical adenitis	5	17	17
17	.....	.....	17	
18	Cervical adenitis	5	17	17
19	.....	.....	17	

plication rate for the patients treated with sulfadiazine was 70 per cent. (Table IV.)

Penicillin Treatment. The group treated with penicillin totaled seventy-four patients. Penicillin was used initially in the cases of more severe illness since it was early known that the offending strain of streptococcus was resistant to sulfadiazine. Later in the season, in order to avoid overtreatment of individuals sensitive to sulfadiazine, penicillin was given to the patients who had received sulfadiazine prophylactically.

Initially, the patients in the penicillin group were treated with 25,000 units intramuscularly every three hours. Treatment was continued for twenty-four hours after the temperature fell to normal. The dosage averaged 425,000 units in three days. The initial results were dramatic. The soreness and swelling of the throat subsided in twelve to twenty-four hours, so that the patient could comfortably swallow solid food at the end of the first day. Evidences of toxicity subsided in this period. The rash continued to spread to the extremities but was less intense. The rash on the trunk began to fade in twenty-four hours with total disappearance in three to four days, in contrast to six to seven days in the cases in which treatment was symptomatic. This suggested that toxin formation in the pharynx had diminished or ceased owing to penicillin treatment and that the spread of the rash was due to the dissemination of the toxin already liberated. However, as the season progressed and the number of complications increased, despite the initial favorable response to the drug, it was decided that administration of penicillin was being discontinued too soon, without complete destruction of the offending organism. This was in keeping with the experience of Plummer. Later, alternate patients were treated for seven to ten days, the total dosage ranging from 1,000,000 to 1,760,000 units of penicillin, with gratifying results as shown in Table VII.

Daily throat cultures were taken on patients receiving penicillin. It was observed that the initial cultures, those positive for beta-hemolytic streptococci, became negative after one day of penicillin therapy and remained negative during the period of treatment. However, a large proportion of

TABLE VI

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED WITH SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS

Case	Day in Hospital																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
20	17	0	17	17	17	17	0	..	17	..	17	17	..	..	..	..	..	17								
21	..	17	17	..	0	17	17	0	17	17	0	17	17	17	17	..	..	17	..	..	..	..	..	..	19	
22	17	17	17	17	17	17	17	0	0	17	17	17	0	..	17	17	17	17	..	..	17					
23	..	..	17	0	17	17	17	0	0	17	17	17	17	17	..	..	NT	..	..	17	..	..	..	17		
24	..	17	17	17	17	17	0	19	17	17	0	0	17	NT	0	0	0	17	17	17	17	..	..	17		
25	..	17	17	17	17	17	17	17	17	+	17	17	17	8	17	17	17	17	17	..	..	..	17	..	..	0
26	..	17	..	..	0	..	17	0	0	0	17	17	17	17	17	..	..	17	..	..	17					

N.B.: NT = No type; + = Culture lost before grouping or typing was done.

TABLE VI—(*Continued*)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED WITH SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS

Case	Total Sulfadiazine, Gm.	Complication	Day of Complication	Initial Type	Complicating Type
20	36	Sulfadiazine reaction	9	17	
21	32	.....	..	17	
22	32	.....	..	17	
23	18	Sulfadiazine reaction	4	17	
24	32	.....	..	17	
25	34	Cervical adenitis	5	17	17
26	..	.....	..	17	

the cultures became positive one or two days or more after the cessation of treatment. This would indicate incomplete sterilization of the throat or reinfection, since the patients were kept in an open ward during the convalescent period. In a few patients who received large doses of penicillin after an initial ten-day period of symptomatic treatment, the throat cultures became permanently negative for hemolytic streptococci. This suggests that when some tissue immunity is built up against the streptococcus, the additional sterilizing effect

TABLE VII

COMPLICATIONS AFFECTING ALTERNATE PATIENTS RECEIVING RESPECTIVELY SYMPTOMATIC TREATMENT AND PENICILLIN

	Symptomatic Treatment	Penicillin Treatment
Cases	15	15
Complications		
Secondary tonsillitis	0	2
Cervical adenitis	5	2
Suppurative otitis media	4	0
Paranasal sinusitis	1	0
Secondary pneumonia	1	0
Peritonsillar abscess	1	0

TABLE VIII

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCUS IN PATIENTS WITH SCARLET FEVER TREATED WITH (A) SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS; (B) PENICILLIN SUBCUTANEOUSLY, 100,000 UNITS ON THE TENTH, ELEVENTH AND TWELFTH DAYS AND (C) SULFADIAZINE, 1 GM. DAILY ON THE THIRTEENTH THROUGH THE TWENTY-EIGHTH DAY

Case	Day in Hospital*																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28	29	33	34	35	37
27	0	17	..	17	17	17	17	17	..	..	17	..	0	0	0	0	0	0	0	0												
28	..	..	17	0	..	17	17	17	..	17	17	17	0	NT	..	..	17	..	..	+	..	..	..	17								
29	17	17	17	17	0	0	17	17	17	0	17	0	0	0	17	..	..	..	..	..	17	..	..	..	17							
30	..	17	17	17	0	17	17	17	0	17	17	0	0	0	0	0	0	0	0	..	..	0	..	..	..	0						
31	..	17	17	17	17	17	0	17	17	0	0	0	0	0	17	0	0	..	..	0	..	..	0	..	..	..	..	..	..	0		
32	..	17	17	0	17	17	19	0	17	17	0	0	0	0	17	17	17	17	..	..	17	..	17	17	..	..	0	..	17	..	0	
33	NT	..	17	17	17	17	17	17	17	17	0	0	17	0	17	17	19	17	17	17	17	..	..	17								
34	..	B	17	17	17	17	17	17	17	17	0	0	..	0	0	0	17	0	17	17	17	..	..	..	..	17	..	17	0	..	..	17

* Days 27, 30, 31, 32 and 36 are omitted since no cultures were taken on these days.
N.B.: NT = No type; B = Group B streptococci; + = Culture lost before grouping or typing was done.

TABLE VIII—(*Continued*)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCUS IN PATIENTS WITH SCARLET FEVER TREATED WITH (A) SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS; (B) PENICILLIN SUBCUTANEOUSLY, 100,000 UNITS ON THE TENTH, ELEVENTH AND TWELFTH DAYS AND (C) SULFADIAZINE, 1 GM. DAILY ON THE THIRTEENTH THROUGH THE TWENTY-EIGHTH DAY

Case	Total Sulfadiazine, Gm.	Total Penicillin, Units	Complications	Day of Complication	Initial Type	Complicating Type
27	48	960,000	Cervical adenitis	9	17	17
28	48	200,000	.....	..	17	
29	52	300,000	.....	..	17	
30	50	300,000	Cervical adenitis	20	17	?
31	44	300,000	.....	..	17	
32	39	300,000	Cervical adenitis	14	17	17
33	40	300,000	.....	..	17	
34	42	300,000	.....	..	17	

of penicillin is more potent than under other circumstances.

Table IV shows the complications encountered in the seventy-four cases in which penicillin was used. Cervical lymphadenitis appeared after administration of penicillin had been stopped on the fifth to fifteenth day, with local swelling of lymph nodes and rise of temperature. This condition subsided without suppuration under further use of penicillin. Suppurative otitis media occurred in 8.1 per cent of the cases from the fifth to fifteenth day of illness. The drum appeared red and bulging with hemorrhagic bleb formation. In all cases the drum was incised and the patients were treated with additional penicillin for three to seven days. Invariably, the drum healed uneventfully. Nasopharyngoscopic examination by Col. Percy Ross, M.C., revealed marked erythema and edema of the posterior nasopharynx with edema of the tissues

TABLE IX

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 200,000 UNITS PER DAY FOR THREE AND FOUR DAYS AS SHOWN BY BOXED AREAS

Case	Day in Hospital																																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
35	..	17	17	0	0	0	..	..	0	..	0	0	0	0	0	0	0	0	0																
36	17	0	0	..	..	17	..	..	17	..	..	..	17	..	..	17	..	..	..	17																
37	..	17	..	..	17	..	..	..	..	..	..	17	..	..	+	..	..	..	17	..	..	..	+	..	..	0	+								
38	..	..	..	..	..	..	17	..	..	..	17	..	..	17	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	17
39	17	..	..	..	..	..	..	0	..	..	17	..	..	..	17																				
40	..	C	..	17	17	0	..	..	0	..	..	17	..	..	..	17	..	..	17	+	..	..	+												
41	..	17	0	..	..	..	17	..	..	0	..	..	..	+																					
42	17	..	..	0	..	..	..	0	..	..	..	0	..	..	..	0																			
43	17	..	..	..	..	0	..	..	..	17	..	..	17	..	..	..	17																		
44	..	17	0	17	..	..	..	17	..	..	0	..	..	..	+																				
45	..	17	..	17	..	..	..	..	..	..	17	..	17																						
46	17	0	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	C															
47	..	17	17	0	0	17	17	17	17	17	17	17	17	C	B	17	17	17	NT	17	17														
48	17	17	..	0	0	0	0	0	0	0	17	17	17	17	17	17	B	17	0	17	17	17	17	17											
49	..	..	17	0	0	17	17	17	17	B	17	17	0	0	0	17	17	17	17	17	17	17	..	17	..	17	17	17	17						
50	17	B	0	17	17	17	17	17	17	17	17	0	17	17	17	0	0	0	17	0	B														
51	0	..	0	0	0	17	0	17	17	17	17	17	..	..	17	..	17	19	0	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	17
52	..	0	17	0	0	..	..	17	..	..	17	17	17	17	0	17	17	0	..	..	..	0													
53	17	..	..	..	..	..	..	..	..	..	..	..	..	17	17	..	17	17	17	17	17	17	17	17	17	..	17	17	17	17	17	17	17	17	17	17
54	..	17	..	17	17	..	17	17	17	17	17	17	0	17	17	17	17	0	17	17	17	17	17	17	..	..	..	..	B	17	0	17			
55	..	0	..	..	17	0	0	17	17	17	17	17	17	17	NT	17	0	..	17	17	17	17	..	..	..	..	..	..	..	..	..	..	19	..	17
56	17	17	0	17	17	17	17	17	17	17	17	17	17	G	17	17	17	17	19	0	17	17	17	..	17	+	17	17	17						
57	..	0	..	..	0	0	17	17	0	17	19	17	17	17	17	0	17	17	C	17	0	0	0	17	17	17	17	17	17	17	17				
58	..	17	0	0	17	17	E	17	C	B	17	17	17	17	0	0	17	17	17	17	17	0	17	..	..	..	..	..	..	17	17				
59	..	0	0	0	G	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	0	17	0	17	0	0	17	17	0						
60	..	17	0	0	0	17	17	17	17	17	17	17	17	17	0	17	17	0	17	17	17	0	17	..	17	17	17	0	0	0	17				
61	..	17	0	0	0	17	17	17	17	0	17	17	0	17	17	17	0	0	17	0	..	0	0	17	0	0	..	..	..	..	..	..	17	..	17
62	..	0	0	17	17	17	17	17	17	17	0	17	17	17	0	0	17	0	17	0	17	17	17	0	17	..	..	17							

N.B.: B = Group B; C = Group C; E = Group E; + = Culture lost before grouping or typing was done.

TABLE IX—(*Continued*)
RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 200,000 UNITS PER DAY FOR THREE AND FOUR DAYS AS SHOWN BY BOXED AREAS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
35	500,000	.....	..	17	
36	300,000	.....	..	17	
37	375,000	.....	..	17	
38	425,000	.....	..	17	
39	525,000	.....	..	17	
40	650,000	.....	..	17	
41	800,000	.....	..	17	
42	625,000	.....	..	17	
43	300,000	Cervical adenitis	8	17	17
44	300,000	.....	..	17	
45	425,000	Cervical adenitis	5	17	17
46	375,000	.....	..	17	
47	400,000	.....	..	17	
48	300,000	.....	..	17	
49	700,000	.....	..	17	
50	200,000	.....	..	17	
51	350,000	.....	...	17	
52	275,000	.....	..	17	
53	475,000	Otitis media	4	17	17
54	400,000	Cervical adenitis	13	17	17
55	300,000	.....	..	17	
56	675,000	Sinusitis	11	17	17
57	650,000	Sinusitis	11	17	19?
58	675,000	Cervical adenitis	11	17	17
59	500,000	Rheumatic fever	21	17	17
60	475,000	.....	..	17	
61	400,000	.....	..	17	
62	275,000	.....	..	17	

surrounding the eustachian tube. Paranasal sinusitis subsided under topical shrinkage of the nostrils and the use of penicillin. Secondary bronchopneumonia, which occurred in six cases, has been discussed under the heading "Streptococcal pneumonia." Rheumatic fever developed in one case in which the patient had received 500,000 units of penicillin during the first three days of scarlet fever. In this case the scarlet fever was severe as manifested by hemorrhagic rash. One soldier had a recurrence of malaria on the twenty-first day of his illness.

ANALYSIS OF PENICILLIN THERAPY

The description of the penicillin treatment series given in the preceding section applies to all cases in which penicillin was used, regardless of the amount received or the regimen of therapy of a particular patient. It is therefore not an entirely fair evaluation.

During the early phases of this study we were searching for the best methods of giving the drugs that were available for the treatment of scarlet fever and its complications. The series are not larger for two reasons. The first was the number of patients available for study; the second was the limitation in the supply of penicillin at the time of study. Data on eighty-seven patients treated with penicillin are analyzed in the following tables.

Each series of cases is presented with a table in which the period of treatment is indicated by boxed squares, the persistence of positive throat cultures is indicated by the type of streptococcus isolated and the total dosage of drugs is given in units or Grams. The complication, day of complication, and complicating type (if known) of streptococcus are also indicated.

Table VIII represents a series of eight patients who were first treated with 4 Gm. a day of sulfadiazine for eight days with the clinical response already noted. The effect on the throat cultures was negative. On the

tenth, eleventh and twelfth days these patients received 100,000 units of penicillin. All of these patients developed negative throat cultures while under this treatment. Two of the patients continued with negative cultures, six reverted to positive. It is interesting that the complications, in two of the three cases in which they occurred, developed late, on the fourteenth and twentieth days, respectively. Complications occurred in three cases, or 37.5 per cent. The ineffectiveness of this treatment in controlling carriers is evident.

Table IX lists twenty-eight patients who were treated intramuscularly with 200,000 units of penicillin per day for three and four days. In general, though not consistently, there was a temporary suppression of the positive throat cultures during the period of treatment, which rapidly disappeared when administration of the drug was discontinued. In this series complications occurred in eight cases, or 28 per cent. In six cases the complications occurred on the eighth day of hospitalization or later. For the most part they were preceded by long persistent periods of positive throat cultures.

Ineffectuality of this treatment in controlling the carrier state is evident.

Table x lists eleven patients who received penicillin treatment during two separate periods. In the first period they received 200,000 units per day for two to four days; in the second period 100,000 units daily, on the tenth, eleventh and twelfth days of their disease. This was followed by 1 Gm. of sulfadiazine daily for thirteen to eighteen days. In this group the initial period of ad-

TABLE X

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WHO RECEIVED PENICILLIN 200,000 UNITS DAILY FOR TWO TO FOUR DAYS INITIALLY AND 100,000 UNITS DAILY ON THE TENTH, ELEVENTH AND TWELFTH DAYS FOLLOWED BY 1 GM. OF SULFADIAZINE DAILY FOR THIRTEEN TO EIGHTEEN DAYS

Case	Day in Hospital																																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
63	..	17	B	0	0	17	17	17	C	0	0	0	0	0	0	0	0	0	0	0	..	0	0	0	0	0	..	..	..	..	..	..	0	..	0
64	..	17	..	0	17	17	17	17	..	..	0	..	0	17	17	17	17	17	17	17															
65	17	17	17	17	17	17	17	17	0	0	0	17	17	17	0	17	17	B	17	..	15	17	17	..	0	..	B	19	17						
66	17	17	17	17	19	17	17	17	17	0	17	17	0	0	0	17	17	17	17	17	..	..	17	..	..	17	..	..	..	..	..	..	..	..	17
67	..	17	0	17	17	17	17	17	17	0	0	0	17	17	17	17	17	17	NT	NT	0	0	17	17	17	17	17	..	..	17	17				
68	..	17	..	17	NT	0	0	0	0	B	B	0	0	0	5	0	17	17	17	17	17	0	17	17	17	0	0	0	..	17	17	..	..	..	17
69	..	0	0	17	17	0	B	19	17	0	0	0	0	0	0	0	..	0	0	0	0	0	17	17	0	..	..	..	..	..	..	..	..	..	0
70	..	17	..	17	0	17	17	17	17	19	0	17	0	0	0	17	17	17	0	0	17	..	17	17	17	17	17	17	17	..	..	17			
71	17	17	..	17	17	17	17	17	17	0	0	17	17	17	0	17	17	17	17	17	17	..	..	..	..	..	17	17	0	17	19	0	..	..	..	0
72	..	..	0	0	0	19	0	0	0	0	0	0	0	0	0																				
73	19	..	19	19	19	19	17	19	0	17	0	19	0	17	19	19	17	19	17	0	17	..	19	17	17	..	..	17	..	..	..	0			

N.B.: NT = No type; B = Group B streptococci; C = Group C streptococci.

TABLE X—(*Continued*)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WHO RECEIVED PENICILLIN 200,000 UNITS DAILY FOR TWO TO FOUR DAYS INITIALLY AND 100,000 UNITS DAILY ON THE TENTH, ELEVENTH AND TWELFTH DAYS FOLLOWED BY 1 GM. OF SULFADIAZINE DAILY FOR THIRTEEN TO EIGHTEEN DAYS

Case	Total Penicillin, Units	Total Sulfadiazine Gm.	Complications	Day of Complication	Initial Type	Complicating Type
63	575,000	18	.....	..	17	
64	700,000	18	Sinusitis	9	17	17
65	600,000	13	Cervical adenitis	6	17	17
66	550,000	13	Cervical adenitis	8	17	17
67	650,000	16	.....	..	17	
68	1,000,000	18	Otitis media	3	17	17
69	625,000	18	.....	..	17	
70	700,000	18	.....	..	17	
71	575,000	18	Cervical adenitis	8	17	17
72	1,000,000	10	.....	..	19	
73	500,000	18	.....	..	19	

ministration of penicillin did not produce as marked a suppression of positive cultures as in the previous group. (Table IX.) The second period produced a temporary suppression in three cases. Spontaneous elimination of the organism apparently occurred in two cases. Complications occurred in five cases, or 66.7 per cent.

It is obvious in this group also that the dosage of penicillin did not control either the carrier state or the complication rate, which would appear to be associated with it.

Table XI demonstrates eight cases of scarlet fever due to group A, type 17, streptococcus in which 400,000 units of penicillin per day was given for three days. Thereafter the patients received 160,000 units per day for three or more days, as indicated by the boxed areas. It now would appear that the dosage given is beginning to approach a useful range. Not only were the clinical benefits more striking than with the smaller dosages, but it will be seen that there was elimination of streptococci in five of the eight cases.

It would appear, however, that complications were not reduced, but in four cases the complications occurred before penicillin therapy was begun, in one case during the course of therapy and in one case after its completion. The total complication rate was 75 per cent, but in only 25 per cent (two cases) did the complication occur during or after treatment.

In Table XII sixteen cases are summarized in which 400,000 units of penicillin was given for three days and thereafter 200,000 units per day for two to seven days. The dosage here was the highest given and offers several interesting points. In all cases there was a suppression of streptococci during the course of treatment. In seven cases (43.8 per cent) there was practically complete suppression and elimination of streptococci with no development of further complications. In five of the remaining cases recurrence or persistence of streptococci in the nose and throat was associated with the development of complications. In two cases it might be argued that throat cultures again became positive because of the complications. In one case the reappearance of streptococci was not accompanied by complications.

It may be stated, then, that adequate dosage suppresses and eliminates a high percentage of streptococci from potential carriers, and that in carriers late complications are likely to develop.

In Table XIII a group of cases is described in which treatment was with penicillin spray. Although not all patients were followed for as long a period as might be

TABLE XI

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI ON PATIENTS RECEIVING PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS AND 160,000 UNITS PER DAY THEREAFTER AS SHOWN IN BOXED AREAS

Case	Day in Hospital																																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
74	17	.	.	.	17	.	.	.	0	.	.	0	.	.	.	.	.	.	.	0	.	0	0	0	17	C	.	B	.	.	17				
75	.	17	.	.	.	17	.	.	17	.	.	.	17	+	0	.	0	0	0	0	0	0	B	17	1	17	B	B	0	0					
76	17	17	.	.	.	17	.	.	+	.	.	.	17	0	0	0	0	0	0	17	17	17	C	17	17	17	C	17	17	17	17	17	17	17	17
77	17	.	.	.	17	.	.	17	.	.	.	+	0	0	0	0	0	0	.	0	0	0	0	0	0										
78	.	17	.	.	17	.	.	+	.	.	.	+	0	0	0	0	0	0	0	0	0	0	0	0	0										
79	.	.	.	.	.	17	.	.	0	.	.	.	0	.	.	0	.	0	0	0	0	0	0	0	0	0	0	0	0						
80	.	17	.	.	17	.	.	.	17	.	.	17	.	0	.	0	.	0	0	0	0	0	0	0	0	0	0	0	.	0	0	0	0	0	
81	17	.	.	.	0	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.	0	0	0	0			

N.B.: B = Group B streptococci; C = Group C streptococci; + = Culture lost before grouping or typing was done.

TABLE XI—(*Continued*)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI ON PATIENTS RECEIVING PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS AND 160,000 UNITS PER DAY THEREAFTER AS SHOWN IN BOXED AREAS

Case	Total Penicillin, Units	Complications	Day of Complication	Initial Type	Complicating Type
74	1,000,000	Otitis media	5	17	17
75	1,480,000	.....	..	17	
76	1,440,000	Sinusitis, Cervical adenitis	8 5	17 17	17 17
77	1,440,000	.....	..	17	
78	1,440,000	.....	..	17	
79	1,450,000	Otitis media	7	17	17
80	1,225,000	Otitis media	12	17	17
81	1,500,000	Otitis media	14	17	17?

desired, they demonstrate that penicillin spray to the nose and throat in the doses used was not sufficient to eliminate the streptococci. In no case did cultures become negative even during the course of treatment.

In two cases of scarlet fever caused by type 17 hemolytic streptococci and in one case caused by type 19 hemolytic streptococci, penicillin was administered by a continuous subcutaneous drip method. (Table XIV.) In one of the cases caused by type 17, and in the case caused by type 19 there was a temporary suppression of streptococci during the course of administration. In the third case a positive culture was obtained after a three day lapse and one day after administration of the drug was discontinued. In all three cases positive cultures were again obtained.

CROSS INFECTION AND THE CARRIER PROBLEM

The last four patients listed in Table XII are representative of one of the problems

encountered in this study. Such patients, even after long periods of freedom from positive cultures, again had streptococci in their throats and nasopharynges. Did they harbor the organisms during this interval, or did they become infected again during convalescence? It is believed that both conditions were operative. Those individuals who regularly carried the organisms consistently continued to have nasopharyngeal pathologic manifestations and undoubtedly belong to the "dangerous carrier" group of Hamburger. Others undoubtedly carried the organisms in their ears, sinuses and elsewhere, and had hidden infections which were not reflected by culture.

That cross infections occurred is seen in many of the cases presented in the tables. Odd incidental types were isolated from throats from which a simple type only had previously been found. Cross infection with type 19 was most common. DeLamater and his associates have described the cross infection rate during the epidemic from which material for this report was derived.

Patients were also studied who had type

TABLE XII

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS, FOLLOWED BY 200,000 UNITS PER DAY FOR TWO TO SEVEN DAYS AS INDICATED BY BOXED AREAS

Case	Day in Hospital																																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
82	17	.	.	.	.	0	.	.	.	0	0	0	0	0	0	0	0																		
83	.	17	0	0	0	0	0	0	0	0	0	0	0	0	0	.	.	0	0	0	.	0	0	0	0										
84	.	17	.	.	0	17	0	0	0	0	0	0	0	0	0	.	.	0	0	0	0	0	0	0	0	0	.	.	.	0						
85	.	17	.	.	0	0	0	0	0	0	0	1	0	0	0	0	0	0	.	.	0	0	0	0	0	0										
86	17	.	.	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	0	0	0	0	0	0	0	0	0	.	.	.	0				
87	.	17	0	+	0	0	33	0	0	0	0	0	0	0	0	.	.	0	0	0	0	0	0	0	0	0	0	0	.	.	0	0	.	.	0	
88	17	0	.	.	.	.	0	.	.	.	0	.	.	.	.	0	0	0	0	.	.	.	.	.	0	0	0	0	0	0	0	0	0	0			
89		0	.	.	.	.	.	.	.	.	.	.	.	.	17	.	.	.	.	.	.	0	.	.	.	.	0	.	.	.	.	.	0	.	.	0	0	17
90	17	.	.	.	0	.	.	.	0	0	17	17	17	17	17	17	17	17	+	+	17															
91					0	17	17	17	17	17	17	17	17	0	+	+	+																			
92	.	.	0	.	.	.	17	0	0	0	0	0	17	17	17	17	17	17	+	.	.	17	17	17	.	.	17	17	17	17						
93	.	.	.	.	.	.	0	.	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	.	.	0	0				
94	17	17	0	.	.	0	0	0	0	0	0	0	0	0	0	0	0	0	.	.	0	0	0	0	0	0	0	0	0	0	17	17	B	B	17	
95	.	17	0	.	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.	.	17	17	17	17	17	17	17	17	17	17	17	.	.	17	17	
96	.	17	.	17	.	.	0	0	0	B	0	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	.	.	17	17	17	17				
97	.	.	.	.	.	0	.	.	0	.	.	17	0	0	0	0	.	.	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	17	17	17	17

N.B.: B = Group B streptococci; + = Culture lost before grouping or typing was done.

TABLE XII—(*Continued*)
RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS, FOLLOWED BY 200,000 UNITS PER DAY FOR TWO TO SEVEN DAYS AS INDICATED BY BOXED AREAS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
82	1,550,000	.....	..	17	
83	1,320,000	.....	..	17	
84	1,340,000	.....	..	17	
85	1,440,000	.....	..	17	
86	1,825,000	.....	..	17	
87	1,760,000	.....	..	17	
88	1,450,000	.....	..	17	
89	2,450,000	Pneumonia	3	?	17
90	1,650,000	Cervical adenitis	15	17	17
91	1,050,000	Cervical adenitis	7	17	17
92	1,140,000	.....	..	17	
93	780,000	Cervical adenitis	15	17	Not demonstrated
94	1,450,000	Mastoiditis	18	17	Not demonstrated
95	1,320,000	Tonsillitis	21	17	17
96	1,625,000	.....	..	17	
97	1,780,000	Tonsillitis	21	17	17

17 streptococci for as long as three months. Had sufficient penicillin been available, an effort would have been made to limit carriers by this means. It is apparent, however, from the foregoing that the amount of penicillin required for such an effort would have been prohibitive.

It would be desirable to have a study made of the effect of penicillin specifically on the so-called "dangerous carrier."

It appears to us that penicillin therapy offers a means for control of carriers provided adequate (large) doses are used over a sufficiently prolonged period.

COMMENT

A study is presented of a series of cases of streptococcal disease, including scarlet fever, all of which were produced by a single strain of group A, type 17, hemolytic streptococcus. The evidence presented may corroborate Keogh in his belief that the relative proportion of the various diseases produced is a characteristic of a given strain.

Because this streptococcus was found to be resistant to sulfadiazine, and because there is evidence (as yet unpublished) to suggest that it became resistant during the early phase of this epidemic which it produced in the face of sulfadiazine prophylaxis, there was added incentive to study its response to other chemotherapeutic agents and antibiotics.

The implication is obvious that if these mutable organisms can become resistant to one antibacterial they may be capable of developing resistance against others. They therefore constitute a threat to existing means of therapy and control. The prophylactic use of drugs (such as sulfadiazine) necessitates the administration of relatively small doses (1 Gm. per day). The low drug levels so produced may be a stimulus to circumventing its action, and so actually aid in the production (or stimulation) of resistant mutants.

That penicillin may have a beneficial clinical effect in low dosage and still not eliminate these organisms completely from the nose and throat is apparent from the work presented. It is obvious that a maximal opportunity is thus given for the organism to produce resistant strains in the presence of the drug, if such is its proclivity.

It is also evident from the data that large doses are relatively more able to eliminate the streptococci and that with their elimination complications become less likely. Clini-

cally this fact alone warrants large initial dosage. It seems likely that even larger unit doses of the drug than those used here are justified, especially since the toxicity of penicillin is so low.

Because of the probability that the organism may be disseminated early to foci not easily eliminated by even large dosage, the earlier the drug is given the better. This can be justified on the basis of the occurrence of complications, as noted in the present study.

How such a program might affect the immunological picture is obscure and needs analysis. That some degree of immunity develops is implied by the relatively milder cases of pneumonia which occurred as complications secondary to scarlet fever.

The control of respiratory diseases remains one of the most common and difficult problems with which modern medicine must cope. The carrier is a menace, not only because of the droplets he exhales which directly or indirectly are sources of infection, but because of the contamination of the objects he touches. His control is an integral part of the problem as a whole.

It seems implicit in the data that the control of the usual and milder complications which apparently aid in the constitution of a carrier may prove to be one means of at least partial control of the basic problem.

SUMMARY AND CONCLUSIONS

1. The clinical disease produced in epidemic form by a sulfadiazine-resistant group

TABLE XIII

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER RECEIVING: (A) NO INITIAL TREATMENT, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (B) PATIENTS INITIALLY TREATED WITH 200,000 UNITS PER DAY FOR TWO TO FOUR DAYS, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (C) PATIENTS INITIALLY TREATED WITH SULFADIAZINE, 4 GM. PER DAY FOR SEVEN DAYS, LATER TREATED FROM TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY

Case	Day in Hospital: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
98	17	.	.	.	17	.	.	.	0	.	.	.	.	17	.	.	17	.	.	.	.	0	.	17	.	.																					
99	.	.	17	.	.	17	17	17	.	.	.	17	.	17	.	.	0	0	17	17	17	0	.	.	.	.	17	.	.	.	.	.	+	.	.	.	+										
100	.	.	17	.	.	17	17	0	0	17	.	.	.	17	.	.	17	0	17	17	17	17	17	17																							
101	.	.	17	.	.	0	17	17	17	17	.	.	.	0	.	.	0	17	17	17	17	17	17	17																							
102	0	.	.	0	0	0	17	0	17	17	17	17	17	.	.	.	17	.	.	17	19	0	0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	17
103	.	.	0	17	0	0	.	.	.	17	.	.	17	17	17	17	0	17	17	0	.	.	.	0																							
104	0	.	.	.	.	.	.	.	.	0	.	.	.	0	.	.	.	17	17	.	.	17	.	.	0	17	17	17	17	17	+	17	+	17	0	+	+									
105	.	.	17	.	.	17	.	.	.	.	0	.	.	.	G	0	0	.	.	17	0	0	0	0	17	NG	17	0	17	0	0	17	17	+	17	17	17	17	17	17	17	17	17	.	.	17	17	17	17	17
106	0	.	.	17	0	0	.	.	.	0	.	.	17	17	.	.	17	17	0	0	0	19	14	17	17	17	+	17	17	+	+	0	17	17	+	17	17	+	+	17	0	0	17	17	17	17	17
																				17																										
107	.	.	0	.	.	.	.	.	.	.	.	.	.	0	17	17	17	17	.	.	.	17	.	.	17	17	17	0	17	E	0	17	17														
108	17	.	.	17	17	0	17	17	17	17	17	.	.	17	.	.	0	17	17	0	17	17																									
109	.	.	0	17	17	17	17	17	.	.	.	17	.	.	17	CR	17	+	17	17	0	17	0																									
110	.	.	.	0	.	.	17	17	0	17	17	17	17	17	.	.	.	17	.	.	17	17	17	0	.	.	17	0	0	0	.	.	.	.	.	.	0										

N.B.: CR = Cross reaction, positive hemolytic streptococci; NG = NO group, positive hemolytic streptococci; E = Group E streptococci; G = Group G streptococci; + = Culture lost before grouping or typing was done.

TABLE XIII—(*Continued*)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER RECEIVING: (A) NO INITIAL TREATMENT, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (B) PATIENTS INITIALLY TREATED WITH 200,000 UNITS PER DAY FOR TWO TO FOUR DAYS, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (C) PATIENTS INITIALLY TREATED WITH SULFADIAZINE, 4 GM. PER DAY FOR SEVEN DAYS, LATER TREATED FROM TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY

Case	Penicillin, Units		Sulfadiazine, Gm.	Complication	Day of Complication	Complicating Type
	Spray	Subcutaneous				
98	300,000	.....	..	.....	..	
99	360,000	.....	..	.....	..	
100	270,000	900,000	12	Sinusitis	2	17
101	300,000	400,000	1	Sinusitis	9	17
102	180,000	400,000	..	.....	..	
103	300,000	625,000	..	.....	..	
104	300,000	625,000	..	Cervical adenitis, Otitis media	9 2	17 17
105	300,000	1,500,000	..	Pneumonia	11	17
106	300,000	1,500,000	..	Otitis media, Pneumonia	22 14	17 17
107	300,000	.....	28	.....	..	
108	210,000	.....	28	.....	..	
109	270,000	.....	28	.....	..	
110	210,000	.....	28	.....	..	

A, type 17, hemolytic streptococcus is described. The origin of clinical material from a uniform population (age group) and its causation by a single strain of streptococcus afforded a unique opportunity for evaluation of the range of clinical manifestations produced by a single strain.

2. It is believed that this may be additional evidence for Keogh's hypothesis that the clinical range and proportion of disease produced by a given streptococcus are specific characters of that strain.

3. A comparison of the complication rates of the more important clinical diseases caused shows complete parallelism with the relative severity of each clinical entity, the rate being highest for scarlet fever, lowest for "nasopharyngitis" with positive culture.

4. Comparison of the complication rates of three forms of treatment used, that is, symptomatic, sulfadiazine and penicillin, is considered to be significant but the diverse management of the groups treated with penicillin prevents fair comparison.

5. Comparison of the clinical response to penicillin and sulfadiazine shows sulfadiazine to be ineffective, and penicillin, even in what is considered to be inadequate dosage for control of the infection, to be dramatic in its relief of symptoms.

TABLE XIV

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH CONSTANT SUBCUTANEOUS DRIP INJECTIONS OF PENICILLIN, 100,000 UNITS IN 1 LITER OF ISOTONIC SALINE SOLUTION DAILY FOR NINE TO ELEVEN DAYS

Case	Day in Hospital																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
111	..	..	17	0	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	..	..	17	..	17	..	17	..	..	..	17					
112	..	17	..	0	17	17	17	0	0	0	17	0	0	0	..	0	0	0	0	17	17	17	..	..	17	..	..	17	17	+	..	17			
113	..	0	0	0	0	0	0	+	0	0	0	0	19	19	+	19	C	19	19	19	19	17	..	19	19	17	19	B	..	..	..	B	19	19	0

N. B.: B = Group B streptococci; + = Culture lost before grouping or typing was done; C = Group C streptococci.

TABLE XIV—(*Continued*)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH CONSTANT SUBCUTANEOUS DRIP INJECTIONS OF PENICILLIN 100,000 UNITS IN 1 LITER OF ISOTONIC SALINE SOLUTION DAILY FOR NINE TO ELEVEN DAYS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
111	870,000	.....	..	17	
112	900,000	.....	..	17	
113	1,000,000	Tonsillitis	15	19?	19

6. Penicillin was found to be only partially effective in control of the carrier state, and then only in high dosage. The same may be said of the development of complications. It is believed that it is implied in the data, if not clearly demonstrated, that early and continued treatment with large dosage will offer some measure of protection against complications as well as against the carrier state.

7. There is strong evidence that in streptococcal disease complications and the carrier state are closely related.

8. When dealing with mutable or potentially mutable organisms, capable of becoming drug-resistant, early large dosage is indicated. Inadequate small dosage producing ineffective drug levels affords a maximal opportunity for mutable organisms to develop drug resistance.

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Transfer of Beta Hemolytic Streptococci by Shaking Hands*

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THE isolation technic employed in contagious disease hospitals recognizes the possible rôle of hands in the transfer of pathogenic micro-organisms by the strict attention paid to the washing of hands after contact with an infected patient. Our attention was drawn to this problem during a study of "dangerous" carriers of hemolytic streptococci during the war,[1] when it was found that large numbers of these bacteria could be recovered from the hands of nasal carriers, though those of throat carriers exhibiting negative nose cultures yielded very few or none at all. Further investigation revealed that gross contamination could occur instantaneously after blowing the nose. This was demonstrated by a simple test in which a carrier cleansed his hands, blew his nose into a sterile handkerchief, and then washed his hands in sterile broth, an aliquot of which was used for making a pour plate. It was not uncommon to recover hundreds of thousands of hemolytic streptococci by this test.

The hands of a nasal carrier emerged as a major *waystation* for hemolytic streptococci on their route from the carrier to a susceptible host. Their probable rôle in the contamination of secondary reservoirs in bedclothing and floor dust, and indirectly of the air, as well as in the pathogenesis of food-borne epidemics has been discussed in a previous communication.[1] Because of the ubiquity of handshaking as a social custom, it seemed advisable to determine how many of these pathogens might be transferred when a nasal carrier shook hands with an uninfected person.

MATERIAL AND METHODS

The carriers (referred to as "donors") employed in these tests were sailors undergoing primary training at the Great Lakes Naval Training Station, Illinois. They were detected by nose and throat surveys by Lieut. R. F. Platzer of Epidemiology Unit No. 13, and were sent to the University of Chicago for the experiments through the kindness of Captain L. D. Arbuckle, Senior Medical Officer at the Training Station. The uninfected subjects (referred to as "recipients") were normal persons whose nose and throat cultures were negative for hemolytic streptococci.

The procedure was as follows: (1) The recipient washed his hands for two to three minutes with soap and water, using a nail brush. He then soaked them in 70 per cent ethyl alcohol, washed off the alcohol with water and dried the hands with a clean towel. (2) He washed his hands in a basin of sterile broth for sixty seconds. (3) The donor shook hands with the recipient. (4) The donor washed his hands for sixty seconds in a basin containing 200 cc. sterile broth. (5) The recipient washed his hands in another basin containing 200 cc. sterile broth. (6) Aliquots of 0.1 cc. and 0.01 cc. from the donor's basin and 5 cc. from the recipient's basin were employed for making

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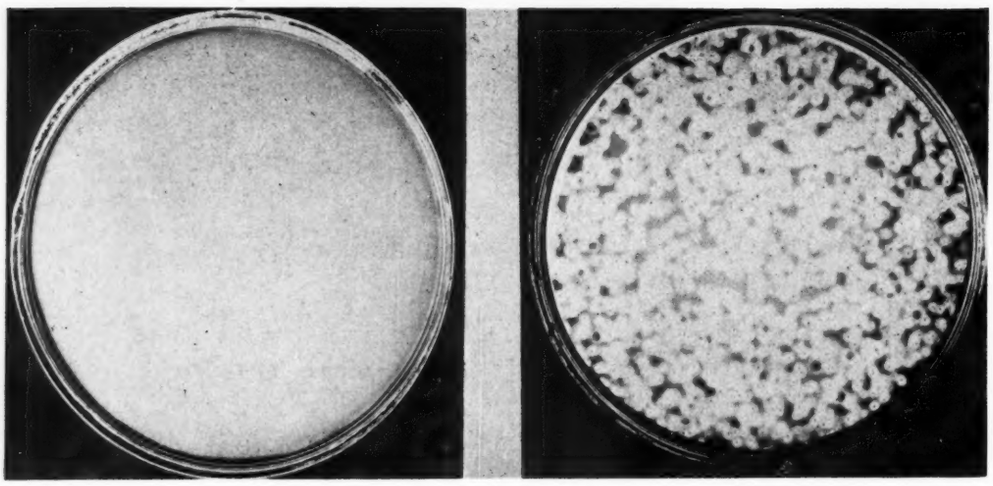

A B

FIG. 1. Cultures of the hands of a non-carrier before, A, and immediately after, B, shaking hands with a nasal carrier of hemolytic streptococci.

blood agar pour plates. The plates were incubated twenty-four hours, following which colony counts for hemolytic streptococci were made.

The serological type of each carrier was determined by the bacteriological staff of Epidermiology Unit 13 by the method of Swift, Wilson and Lancefield.[2]

TABLE I

HEMOLYTIC STREPTOCOCCI TRANSFERRED BY NASAL CARRIERS DURING HANDSHAKING—CARRIER BLEW NOSE IMMEDIATELY BEFORE SHAKING HANDS

Carrier No.	Streptococcal Type	Hemolytic Streptococci Recovered from Sterile Handkerchief into Which Carrier Blew Nose	Hemolytic Streptococci Recovered from Carrier's Hands	Hemolytic Streptococci Recovered from Recipient's Hands	
				Before Shaking Hands	After Shaking Hands
1	17	2,005,000	82,000	0	49,920
2	17	440,000,000	84,000	0	10,560
3	3	75,000	1,640,000	0	> 6,000
4	3	395,000	94,000	0	3,960
5	17	8,960,000	94,000	0	2,520
6	3	45,500	4,000	0	920
7	19	20,000,000	414,000	0	720
8	A	2,160,000	86,000	0	520
9	19	1,120,000	160,000	0	320
10	3	500	122,000	0	240
11	A	1,600,000	22,000	0	80
12	19	15,000	2,000	0	40
13	A	870,000	2,000	0	40
14	3	500	11,000	0	0
15	17	3,260,000	42,000	0	0
16	A	209,000,000	2,000	0	0
17	17	103,000	3,000	0	0
Average			169,000	0	4,450

RESULTS

Table 1 presents the results of seventeen tests in which the donor (carrier) blew his nose just before shaking hands with the recipient. The number transferred varied between none and 49,920, with an average of 4,450. Figure 1 is a photograph of the cultures of recipient No. 1 before and after shaking hands with carrier No. 1. The percentage of donors' streptococci transferred to recipients also varied considerably, but

TABLE II

HEMOLYTIC STREPTOCOCCI TRANSFERRED BY NASAL CARRIERS DURING HANDSHAKING—DID NOT BLOW NOSE IMMEDIATELY BEFORE EXPERIMENT

Carrier No.	Streptococcal Type	Hemolytic Streptococci Recovered from Sterile Handkerchief into Which Carrier Blew Nose	Hemolytic Streptococci Recovered from Carrier's Hands	Hemolytic Streptococci Recovered from Recipient's Hands	
				Before Shaking Hands	After Shaking Hands
18	17	440,000,000	84,000	0	1960
19	Not A	3,160,000	86,000	0	1960
20	A	.....	10,000	..	600
21	A	870,000	2,000	0	480
22	A	1,600,000	22,000	0	40
23	17	2,005.000	82,000	0	40
24	17	8,960,000	94,000	0	0
25	A	200,000,000	2,000	0	0
26	17	103,000	2,000	0	0
Average			43,400	0	564

averaged 2.6 per cent of the number recovered from the donors' hands.

In nine tests in which the donor had not blown his nose for one-half to three hours, fewer streptococci were transferred, the average being only 564 and the range 0 to 1960. These are presented in Table II.

It would appear then that the transfer of streptococci by shaking hands is more likely to occur when the nasal secretion on the hands is still moist.

Review of the tables reveals no direct quantitative correlation between the actual number of streptococci expelled from the nose and those recovered from the hands of any individual carrier, nor between the number on the hands of the donor and of the recipient. This is not surprising since factors such as the viscosity of the secretion, the mechanics of the act of blowing the nose, the dryness or moistness of the hands of both donor and recipient, and the technic and intensity of the handshake will strongly influence the number of streptococci finally transferred. It may or may not be a coincidence that the recipient whose hands were most heavily contaminated during the test was an extremely attractive young woman.

COMMENT

These results demonstrate that one of our oldest social customs, shaking hands, is not free of danger, though it is not our opinion that streptococcal infection is usually acquired by this means. Should a person who has just shaken hands with a nasal carrier put his own fingers into the mouth or nose or should he have a small open cut or other lesion on his own hands, he may, of course, become infected.

The possibility of transmitting both diphtheria and streptococcal infection by contaminated hands was recognized in 1919 by Weaver and Murchie,[3] who were able to recover diphtheria bacilli and hemolytic streptococci from the palmar surface of the right index finger and from beneath the nail of internes and student nurses working in diphtheria wards. Positive cultures were occasionally obtained from door knobs on these wards. In 1926 and 1928, Hill and Matthews[4] and Matthews[5] published the results of experiments showing that hands swabbed with sputum or with cultures of tubercle bacilli, typhoid bacilli or diphtheria bacilli readily transferred the inoculated bacteria to a second person by shaking hands with him. In two of four experiments in which the first person shook hands with the second, the second with the third, and so on, B. prodigiosus swabbed on the hands of the first subject were recovered from those of the fifth.

SUMMARY

Quantitative cultures of the hands of nasal carriers of hemolytic streptococci and of individuals who shook hands with these carriers showed that several hundred to as many as 49,900 of these pathogens could be transferred by ordinary handshakes. The greatest numbers were transferred by carriers who had just blown their noses into sterile handkerchiefs.

We wish to express our thanks to Lieut. R. F. Platzer and the personnel of Epidemiology Unit No. 13 for their cooperation. Valuable technical assistance was rendered by Miss Carol Kraeger.

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Clinical and Pathological Findings in Cases of Truncus Arteriosus in Infancy*

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THE exact definition of a truncus arteriosus has been the subject of considerable discussion. For many years it was maintained that in order for the condition to represent a true truncus arteriosus there must be a single great vessel of abnormally large caliber, guarded by four semi-lunar valves, and the pulmonary arteries should arise directly from this vessel and the coronary arteries should arise from its base. During recent years the general consensus[1,11,15] has been that even though the orifice of the single great vessel may be guarded by two, three or four semi-lunar valves, the condition may still be considered as a truncus arteriosus, provided the coronary arteries arise at its base and the pulmonary arteries are given off from this great vessel.

Humphreys,[11] in her extensive study of this anomaly, presented evidence to show that cases in which the pulmonary arteries failed to meet the ventricles or the aorta, and in which the circulation to the lungs was by way of the bronchial arteries, represented an even earlier arrest in the formation of the great vessels than did a truncus arteriosus in which the pulmonary arteries arose directly from the aorta. She cited one case in which one pulmonary artery arose directly from the aorta and the other pulmonary artery ended blindly. The circulation to the latter lung was by way of the bronchial arteries.

A truncus arteriosus may, therefore, be defined as a single great vessel of abnormally large caliber, from the base of which the coronary arteries arise, and which receives the blood from both ventricles and pumps the blood to the body and to the lungs by way of arterial pathways, i.e., either the pulmonary artery arises directly from the aorta or the circulation to the lungs is by way of the bronchial arteries. In most instances the ductus arteriosus fails to develop; it is never of functional importance.

Although a few cases have been reported in which the individual lived to late childhood[17] or early adult life,[3,14,23] the condition is usually fatal in infancy;[2,5,13,15,22] death frequently occurs within the first week of life. Except for Danelius's[4] report of the absence of the normal hilar "coma" found in cases of truncus arteriosus, virtually no attempt has been made to diagnose the condition during life. The following two cases indicate that in infancy a truncus arteriosus causes the heart to assume a distinctive contour; indeed the contour is so unique that the clinical diagnosis can be made with relative ease.

CASE REPORTS

CASE 1. W. T., (H. L. H. No. 99456), a colored male infant born July 5, 1936, was first seen at the Harriet Lane Home at three and one-half months of age because of heavy breathing, failure to gain weight and diarrhea. Physical examination revealed the temperature to be 37.2°C., pulse 150, respiration 50, weight 2.8

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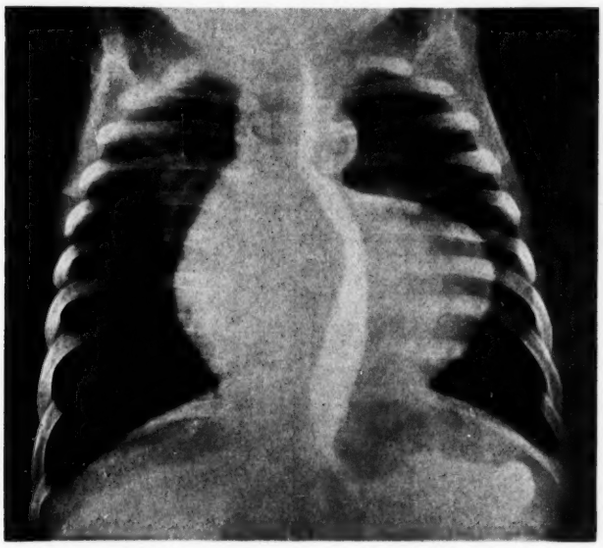

FIG. 1. *X*-ray of heart of Case 1 in anteroposterior view.

kilograms, height 56 cm. The general appearance was that of a markedly emaciated negro infant who was breathing rapidly and who showed slight but definite persistent cyanosis. The heart was enlarged. There was a harsh systolic murmur maximal over the heart which was well transmitted into the vessels of the neck and readily heard all over the posterior thoracic wall. The author thought the murmur was limited to systole; however, opinions on this point differed, and many persons thought there was a continuous murmur which extended throughout systole and diastole. The second sound at the base was accentuated and had the purity which occurs when there is but one great vessel. The lungs were clear. The liver extended halfway to the umbilicus but did not pulsate. There was a strong pulse in the femoral artery. The blood pressure in the arm was 80/50.

Laboratory data showed: red blood cell count 4.9 million per cu. mm., hemoglobin, 14 Gm. per 100 cc.

Fluoroscopic examination revealed a heart with a remarkable contour. In the anteroposterior view there was a sharp angulation of the cardiac shadow to the left of the sternum. There was no visible pulmonary conus; the aortic shadow was narrow but the aortic knob was conspicuous. (Fig. 1.) On rotation of the infant into the left anterior oblique position, the right ventricle appeared greatly enlarged and extended abruptly outward from the aorta to the anterior chest wall. (Fig. 2.) The left ventricle also appeared to be huge.

Upon the administration of barium a sharp angulation of the esophagus was visible at the level of the prominent aortic knob. In addition, the lower part of the esophagus was displaced backward. In the anteroposterior view the displacement of the esophagus was even more striking. In the region of the left auricle it curved markedly to the left. (Fig. 2.)

The electrocardiogram showed relatively high P waves, T_2 given off 2 mm. above the isoelectric line, and the wide ventricular deflection common in congenital malformation of the heart. There was no axis deviation. (Fig. 3.)

The clinical impression was that of a severe congenital malformation of the heart. The contour of the heart in the anteroposterior view distinctly showed a lack of the shadow cast by the normal pulmonary artery, a narrow aortic shadow and a pronounced aortic knob. The left auricle was huge and both ventricles were greatly enlarged. Although in the anteroposterior view the contour of the heart was similar to that of a non-functioning right ventricle, in the left anterior oblique position the contour indicated that the right ventricle was huge. In short, it was a new contour which suggested that there was a pulmonary atresia and that the aorta over-rode both ventricles and enlargement of the left auricle.

The patient failed to gain weight. He became

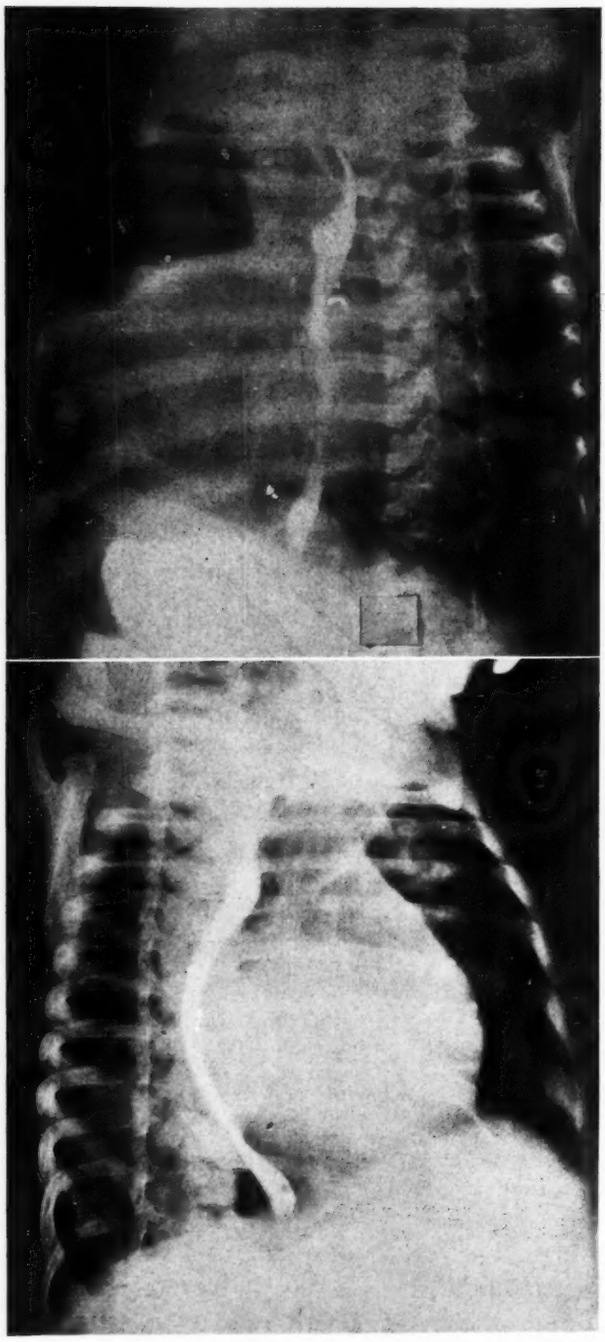

FIG. 2A.

FIG. 2B.

FIG. 2. *X*-ray of heart in Case 1 of left (A) and right (B) anterior oblique positions.

increasingly cyanotic and died of cardiac failure at four months of age.

Autopsy Report No. 15057. (Performed by Dr. Follis.) The heart was greatly enlarged. It measured 5 cm. in transverse diameter and lay more to the right than was normal. The superior vena cava and the inferior vena cava opened normally into the right auricle, which was enlarged. The foramen ovale was completely sealed.

The right ventricle was a relatively small chamber but its wall was enormously hypertrophied; it measured 7 mm. in thickness. There was a defect in the membranous portion

of the ventricular septum. The large aorta arose above the defect. The aortic orifice was guarded by three semi-lunar cusps. The coronary arteries were normal. The pulmonary artery was a small, thin-walled vessel which branched to the lungs in the normal fashion, but ended blindly (Fig. 4) and did not communicate with the heart or the aorta. The ductus arteriosus was absent. No cord or remnant of the ductus arteriosus was found; moreover, there was no puckering in the aorta or the pulmonary artery to show where it had been. The left auricle was greatly enlarged. The left ventricle was larger than the right. It, too, was hypertrophied; its wall measured 9 mm. in thickness. An interventricular septal defect was clearly visible beneath the aorta. The aorta was enlarged; immediately above the aortic valve it measured 4.5 cm. in circumference. It became progressively narrower as it arched posteriorly.

The intercostal arteries were greatly dilated; their orifices were enlarged and the walls of these vessels were thicker than that of the pulmonary artery. The esophagus was found to be caught between the dilated intercostal arteries. (Fig. 4.)

One branch of a bronchial artery was injected and fluid emerged from the pulmonary artery and the pulmonary veins at the same time, which indicated that there was a definite anastomosis between the bronchial artery and the pulmonary artery. The anastomosis of the vessels was so extensive that the injection of the bronchial artery did not permit the differentiation of the bronchial arteries from the pulmonary artery.

Anatomical Diagnosis: Congenital malformation of the heart. Displacement of aorta, pulmonary atresia, high ventricular septal defect, premature obliteration of ductus arteriosus, closed foramen ovale, enlarged bronchial arteries, cardiac hypertrophy, chronic passive congestion and lobular pneumonia.

In brief, the malformation was that of a truncus arteriosus with the circulation to the lungs by way of the bronchial arteries.

Comment. The condition found at autopsy explained the clinical observation of the enlargement of both ventricles, the narrow aortic shadow and the large aorta.

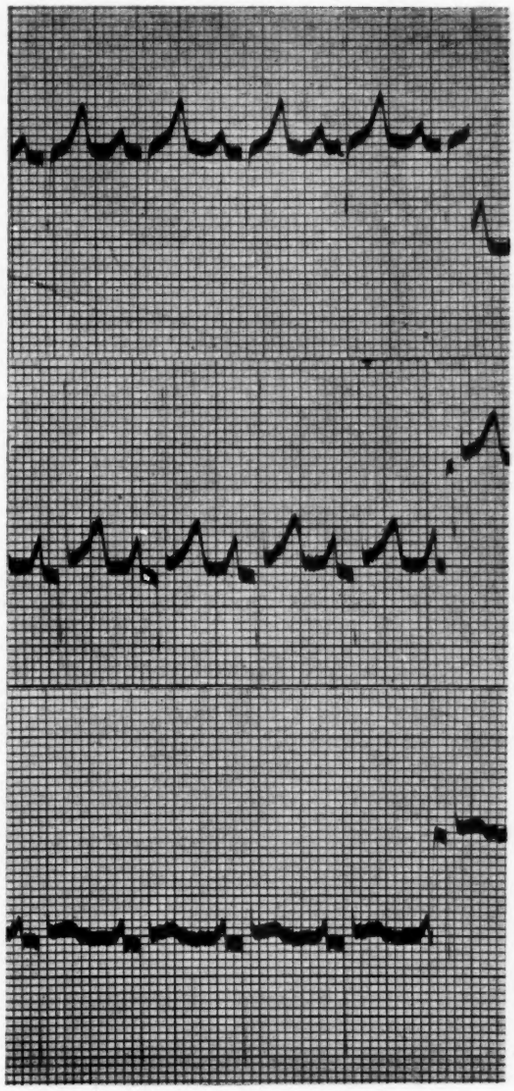

FIG. 3. Electrocardiogram of Case I.

The distortion of the esophagus was in part due to the large left auricle (for which no adequate explanation was ever found) and in part due to the fact that the esophagus was caught between the dilated bronchial arteries.

CASE II. Baby H, a white female infant born February 6, 1943, at the Woman's Hospital was seen in consultation at ten days of age because of a heart murmur. The infant did well for the first week of life and then began to do poorly. Physical examination revealed the pulse to be 140, respirations 30 to 40 per minute. The infant's color was variable. At times it was

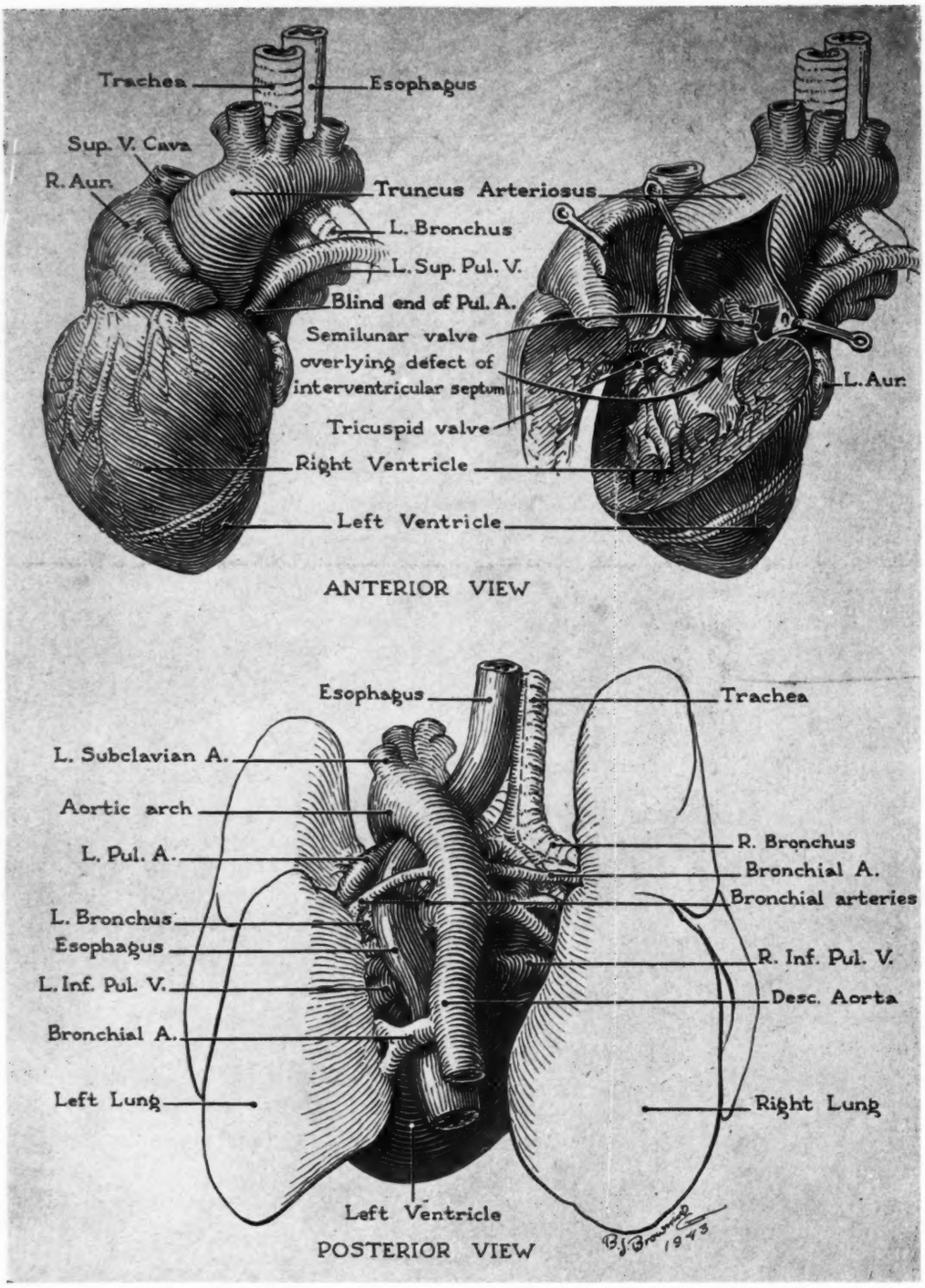

FIG. 4. Drawing of the heart of Case 1; a truncus arteriosus with the circulation to the lungs by way of the bronchial arteries.

normal and then it would become definitely cyanotic. Crying lessened the cyanosis. The heart was enlarged. The heart action was quiet; the sounds were of good quality. The second sound at the base was loud. There was a definite precordial thrill and a harsh systolic murmur was heard all over the chest. The liver extended two fingerbreadths below the costal margin and did not pulsate. There was a strong pulse in the radial artery and in the dorsalis pedis.

Fluoroscopic examination showed the heart to be greatly enlarged. The right auricle was markedly dilated. The pulmonary conus did not appear to be full. In the left anterior oblique position the right ventricle was huge and extended abruptly out to the anterior chest wall. In the right anterior oblique position the esophagram was normal.

The clinical impression was that of a gross defect in the interauricular septum.

Three days later the infant became extremely dyspneic and the liver descended to the umbilicus. The following morning she died. The rapid failure of the circulation indicated a more serious malformation of the heart than an isolated gross defect in the interauricular septum. It was then realized that the abrupt angulation and the great enlargement of the right ventricle seen in the left anterior oblique position was consistent with a truncus arteriosus.

The final clinical diagnosis was: A gross defect in the interauricular septum and a truncus arteriosus with bronchial arteries. This diagnosis was made because of the similarity of the contour of the heart in the left anterior oblique position to that of the first case.

Autopsy. (Performed by Dr. Hellijas.) The heart was enormously enlarged. It extended to the left costal margin and almost filled the right hemithorax. The superior vena cava and the inferior vena cava opened into the right auricle in the normal fashion. There was an enormous defect in the interauricular septum; nearly half of the septal wall was lacking. The tricuspid valve had only two leaflets. The right ventricle was enlarged and its wall hypertrophied. At the base of the interventricular septum was a defect which communicated with the left ventricle. The pulmonary veins opened into the left auricle which was not enlarged. The mitral valve was normal. The interventricular septal defect lay beneath the base of the aorta. A single great vessel, the aorta or truncus arteriosus, arose above the defect in the interventricular septum and thus received blood from both ventricles. The orifice of this vessel was guarded by three semi-lunar valves, and the coronary arteries were given off in the normal manner. The pulmonary arteries were given off directly from the aorta. The ductus arteriosus was absent and there was no indication in the pulmonary artery or in the aorta that it had ever existed.

Final Anatomical Diagnosis: Truncus arteriosus with the pulmonary arteries arising directly from the aorta, a gross defect in the interauricular septum and a high ventricular septal defect.

Comment. Autopsy confirmed the clinical diagnosis of a truncus arteriosus but showed that the pulmonary arteries arose directly from the aorta. The fact that the pulmonary artery arose directly from the aorta explained the occurrence of the transitory and minimal cyanosis.

COMMENTS

The first case is one of a truncus arteriosus with bronchial arteries. In the second case the pulmonary arteries arose directly from the aorta and even though the infant was but two weeks of age, no trace of a ductus arteriosus was found at autopsy. The two cases differed from each other in two important respects; first, in the structure of the interauricular septum, and second, in the pathway by which the blood reached the lungs. In Case I, the circulation to the lungs was by way of the bronchial arteries; consequently, only a small volume of blood reached the lungs for aeration and only a small volume of oxygenated blood was returned to the left auricle and the left ventricle. This blood was mixed with the relatively large volume of blood which was directed to the systemic circulation and was returned by the superior vena cava and the inferior vena cava to the right auricle and the right ventricle. It follows that a small volume of oxygenated blood was mixed with a large volume of unoxygenated blood and only a small volume of oxygenated blood was pumped into the systemic circulation; cyanosis was intense. In the second case the pulmonary arteries arose directly from the aorta and the circulation to the lungs was far more adequate. Indeed, the circulation

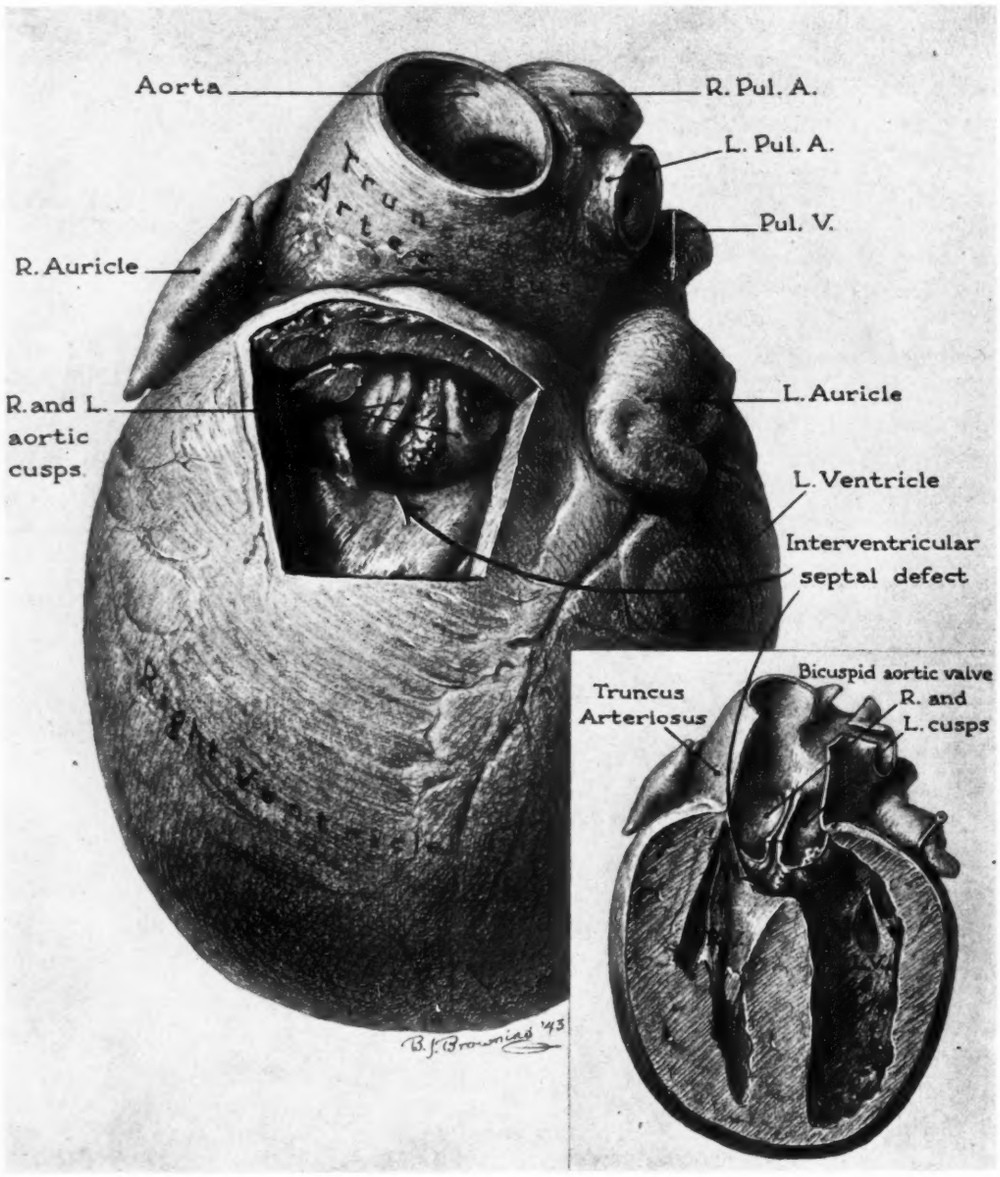

FIG. 5. Drawing of a heart, (illustrative of Case II); a truncus arteriosus in which the pulmonary arteries arise directly from the truncus arteriosus.

was such that when the oxygenated blood returned to the left side of the heart and was mixed with the venous blood returned from the body to the right side of the heart, there was no "visible" cyanosis.

These two cases differed greatly in the structure of the auricular septum. These differences were reflected in the fluoroscopic and *x*-ray findings. In the former, the left auricle was markedly enlarged, whereas in the latter, the right auricle was huge.

The structure of the ventricles was identical in the two cases. In both, the single great vessel arose directly from the two ventricles; consequently, in both instances there was a high ventricular septal defect. The structure of the heart in Case I is illustrated in Figure 4; a counterpart of Case II is shown in Figure 5, which, although drawn from a different specimen, is an exact replica, except that in Case II there was in addition a gross defect in the interauricular septum.

It is of interest and of significance that the contour of the ventricles in these two cases was identical. In Case II in the antero-posterior view the absence of the normal fullness of the pulmonary conus was not as striking as in Case I. Nevertheless, in the left anterior oblique position the right ventricle extended abruptly out from the aorta to the anterior chest wall as a shelf. To the best of my knowledge no other malformation causes such an abrupt shelf. Such a contour visualized in the left anterior oblique position is virtually diagnostic of a truncus arteriosus.

There are, in addition, two other features which aid in the establishment of the correct diagnosis. The first is the abnormally large aorta and the prominent aortic knob. A prominent aortic knob is rare in infancy. Indeed, normally the aortic knob is hidden behind the sternum. A large aorta should always arouse suspicion of the possibility of a truncus arteriosus. The second feature is one which Danelius[4] has emphasized, namely, the absence of the normal "coma" shadow. In my experience diminished hilar shadows are common in all malformations in which there is diminished blood flow to the lungs. It is seen in a truncus arteriosus with bronchial arteries but not when the pulmonary artery arises directly from the aorta.

The clinical feature which most sharply differentiates these two types of truncus arteriosus is the presence or absence of cyanosis. When the circulation to the lungs is through the bronchial arteries, cyanosis is intense; whereas, when the pulmonary arteries arise directly from the aorta, there is adequate circulation to the lungs and cyanosis is minimal or absent. Nevertheless, the contour of the heart in the two conditions is identical.

SUMMARY

Two cases of truncus arteriosus in infants are reported. In the first case the circulation to the lungs was by way of the bronchial arteries and cyanosis was intense. In the second case the pulmonary arteries arose directly from the aorta; consequently, there was adequate circulation to the lungs and cyanosis was absent.

In both cases the contour of the heart in the left anterior oblique position was identical. In each instance the right ventricle extended out abruptly from the aorta to the anterior chest wall as a shelf. At autopsy the structures of the ventricles and their relation to the truncus arteriosus were found to be identical. Therefore, the author believes that this contour is characteristic of a truncus arteriosus in infancy in which the ventricles are normally formed and in which the aorta over-rides the ventricular septum and receives blood from both ventricles.

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Influenza*

A Preliminary State-wide Survey Using Routine Blood Specimens

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THE quarter of a million blood specimens sent to this laboratory each year for serologic examination for syphilis should reflect the immunologic status of the residents of New York as regards various infectious diseases. They are reports from the field and may carry considerable information of value to health officers. Thus they might serve to reveal the prevalence and distribution of certain infectious diseases which are unreported or difficult to identify clinically. The suitability of the plan in the case of a particular disease would vary with the specificity and sensitivity of available technics and the ability to assemble samples which correctly represent the population being studied.

With these thoughts in mind, in the spring of 1945 we initiated the collection of pools of sera for a preliminary survey of the influenza antibody titer of persons living in New York State. Influenza seemed particularly suited to such an inquiry because of the established importance of laboratory diagnosis and the rather clear picture that has now been drawn of the significance of such information. Regarding the latter, it is only necessary to point out that the criterion of "excess pneumonia mortality"[1] does not distinguish between epidemics caused by influenza viruses A and B, while the apparent incidence of influenza is commonly distorted by the concurrence of other clinically indistinguishable upper respiratory infections.[2] The value of serologic tests has been demonstrated in many investigations. The rise of antibody levels after infection and epidemics and their slow fall thereafter[3] are well known, as is also the relative susceptibility of individuals with low-titered sera.[4] Serologic tests have served to identify the incitant of many outbreaks of the disease in recent years and to evaluate the results of vaccination[5] but they have not been methodically applied in a routine manner to so large an area as New York State (exclusive of New York City).

Finally, it should be noted that the fact that the periodicity of influenza may be explained by separating the cycles of influenza A and B and that these cycles may depend on the antibody status of the population[6] give added interest to a continuous state-wide survey.

The material so far examined includes three series of 300 to 350 pools, each of five sera. The first series was collected during the early summer of 1945; the second series, the following December, at the beginning of an epidemic of mild influenza; and the third series in the latter part of January and early February of 1946.

The pools consisted of specimens that did not react in the complement-fixation test for syphilis. For the most part, the more densely populated counties were represented by four urban and four rural pools, the less populous by four rural pools only. For this

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TABLE I

TYPE-A AND TYPE-B INFLUENZA ANTIBODY TITERS OF ACUTE- AND CONVALESCENT-PHASE HUMAN SERA DETERMINED BY HEMAGGLUTINATION-INHIBITION AND BY COMPLEMENT FIXATION

Location of Cases	No. of Case	Age of Patient	Date of Onset	No. of Specimen	Date of Collection	Hemagglutination-inhibition Titer		Complement-fixation Titer	
						A(PR8)	B(Lee)	A(PR8)	B(Lee)
Kingston	1*	13	12/8/45	M7270	12/9/45	81	45	<2.0	<2.0
				R46-138	1/8/46	91	512	4.6	70
	2	13	12/8/45	M7269	12/9/45	203	64	5.7	<2.0
				R46-154	2/5/46	203	128	6.1	22
	3	35	12/12/45	R45-390	12/14/45	32	45	<2.0	<2.0
				R46-135	1/7/46	111	456	4.5	74
	4	52	12/6/45	M7271	12/9/45	181	23	17	<2.0
				R46-136	1/8/46	294	194	13	36
Ithaca	5	27	12/5/45	M7239	12/8/45	128	128	7.6	4.9
				R46-144	1/21/46	128	724	8.9	53
	6	21	12/5/45	M7240	12/8/45	223	256	7.4	13
				R46-143	1/21/46	256	813	6.5	47
	7	18	12/6/45	M7230	12/8/45	1290	256	9.8	6.7
				R46-139	1/21/46	724	645	4.3	>12
	8	18	12/4/45	M7242	12/8/45	362	64	7.9	<2.0
				R46-141	1/21/46	194	512	6.1	81
	9	21	12/4/45	M7244	12/8/45	304	91	8.1	<2.0
				R46-147	1/21/46	304	431	7.1	29
	10	19	12/4/45	M7232	12/8/45	256	6888	4.0	32
				R46-149	1/22/46	181	4096	4.5	30
	11	36	12/3/45	M7241	12/8/45	256	128	12	11
				R46-148	1/22/46	323	181	14	54
	12	17	12/3/45	M7228	12/8/45	362	181	6.3	<2.0
				R46-142	1/21/46	323	813	5.7	54
	13	20	12/3/45	M7234	12/8/45	128	91	12	11
				R46-152	1/22/46	152	1024	7.2	66
	14	19	12/2/45	M7229	12/8/45	208	181	9.0	<2.0
				R46-151	1/21/46	256	446	9.8	44
	15	21	12/2/45	M7245	12/8/45	161	128	12	<2.0
				R46-150	1/21/46	256	1024	7.5	33
	16	41	12/1/45	M7236	12/8/45	64	256	6.0	46
				R46-140	1/17/46	91	645	4.4	55
	17	17	11/30/45	M7231	12/8/45	512	1024	15	296
				R46-145	1/22/46	323	645	15	59
Albany County	18	13	12/10/45	M7317	12/11/45	114	23	10	<2.0
				R46-73	1/3/46	23	32	6.1	2.6
	19	12	12/10/45	M7314	12/11/45	114	45	5.0	2.2
				R46-71	1/3/46	45	84	2.9	1.5
	20	10	12/10/45	M7315	12/11/45	56	23	8.5	<2.0
				R46-67	1/3/46	74	23	3.6	<2.0
	21	8	12/9/45	M7316	12/11/45	128	45	9.2	<2.0
				R46-74	1/3/46	64	64	7.2	2.1
	22	8	12/8/45	M7313	12/11/45	102	23	<2.0	<2.0
				R46-69	1/3/46	47	23	3.8	1.7
	23	8	12/5/45	M7312	12/11/45	32	23	<2.0	<2.0
				R46-70	1/3/46	16	16	<2.0	<2.0
	24	9	12/4/45	M7311	12/11/45	215	45	7.2	4.0
				R46-72	1/3/46	105	114	5.6	7.5
	25	8	12/4/45	M7310	12/11/45	91	40	4.4	<2.0
				R46-68	1/3/46	49	23	3.4	<2.0

* Influenza-B virus isolated.

study, centers with a population of 10,000 or over were classified as urban, those with less than 10,000 population as rural.

Serum specimens were also collected in December, 1945, during the acute and convalescent phases of infection from groups of patients in Kingston, Ithaca, and Albany County who had symptoms of acute upper respiratory disease tentatively diagnosed as influenza.

The sera were tested by Hirst's hemagglutination-inhibition technic[7] and the quantitative complement-fixation test developed in this laboratory,[8] which we have adapted to influenza.[9] The titers of the latter are expressed in terms of the maximum amount of complement required for 50 per cent hemolysis by a fixed quantity of serum (0.05 ml.) in the presence of antigen.

RESULTS

Sera from Patients. The patients' sera yielded, in general, similar results with both technics. (Table I.) When compared with sera taken during the acute phase, none of the convalescent sera showed significantly increased titers for influenza-A virus by either method of testing. With the hemagglutination-inhibition technic, convalescent sera from all of the Kingston cases and seven of the thirteen Ithaca patients exhibited four-fold rises when tested with influenza-B virus, and three other Ithaca patients showed a two- to three-fold rise. In the complement-fixation test, the Kingston sera and ten of the Ithaca specimens showed marked increases in titer with influenza-B antigen; three of the Ithaca acute-phase sera had high titers and a rise was not demonstrated in the convalescent-phase specimens. The Albany sera, all of which came from children in one institution, did not show increased titers with either influenza-virus A or B by either method.

These results furnish data concerning the nature of the epidemic that occurred in New York State during December, 1945. Evidently in the two areas in which influenza was diagnosed, the disease was due to influenza-virus B. Also, throat washings were examined for the presence of virus by amniotic inoculation of embryonated eggs and influenza-B virus recovered from one. This is of relatively little weight in determining the causative factor but is harmonious with the serologic evidence and general experience that the epidemic was predominantly due to influenza-B virus.

Pooled Sera. In contrast to the results obtained with the sera of patients, a considerable difference was obtained in the results when the pooled sera were tested by the two methods. Judged by the hemagglutination-inhibition method, there was little difference in the mean titers for influenza virus A and B for the three series. (Table II.) However, the proportion of pools in the second and third series with titers over 512 with influenza-virus A and B was lower than in the first series.

TABLE II
INFLUENZA-A AND -B ANTIBODY TITERS IN POOLED HUMAN SERA DETERMINED BY THE HEMAGGLUTINATION-INHIBITION TECHNIC

Series	No. of Pools	Antigen	Maximum Titer	Mean Titer	Per Cent with Titers of		
					<128	128–512	>512
I	349	A	912	336	12.0	71.4	16.6
II	348	A	1024	232	25.1	69.0	5.9
III	307	A	1024	290	7.5	85.9	6.6
I	349	B	840	274	28.2	55.1	16.6
II	348	B	1623	199	53.3	44.1	2.5
III	307	B	1448	209	32.1	65.3	2.6

The mean titers by the complement-fixation method were not markedly different in the three series. More strikingly the proportion of pools having high titers, that is above 10, with influenza-virus B antigen rose from 4.3 per cent to approxi-

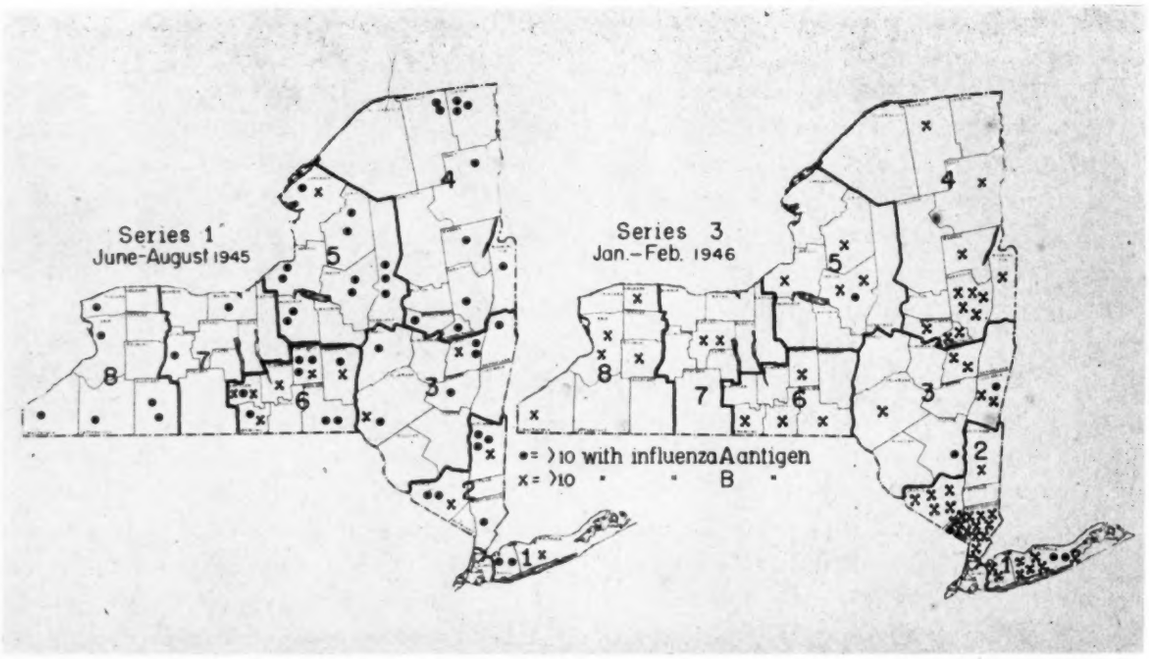

FIG. 1. Distribution of pools of sera with complement-fixation titers of over 10 with influence-A and -B antigens.

mately 18 per cent in the third series, whereas the proportion of pools with high titers for influenza-virus A fell from 16.3 to 2.3 per cent. (Table III.)

TABLE III
COMPLEMENT-FIXATION TITERS OF POOLED HUMAN SERA COLLECTED IN 1945 AND 1946

Series*	Antigen	No. of Pools	Maximum Titer	Mean Titer	Per Cent with Titers of		
					<5.0	5–10	>10
I	A	349	38	7.7	24.9	58.8	16.3
II	A	348	21	5.3	52.0	38.5	9.5
III	A	307	17	4.6	67.1	30.6	2.3
I	B	349	22	6.5	37.2	58.5	4.3
II	B	348	30	5.3	57.3	35.1	7.4
III	B	307	102	8.0	41.4	40.7	17.9

* Series I collected June-August, 1945.
Series II collected December, 1945.
Series III collected January-February, 1946.

If the results of the complement-fixation tests are analyzed geographically (Fig. 1) it will be seen that the pools in the first series with high influenza-B titers were principally from medical region 6, whereas in the third series, they tended to be grouped in those counties bordering New York City with smaller foci elsewhere. In the first series, pools with high influenza-A titers were scattered throughout the state; in series three, they were almost all in or close to regions 1 and 2.

COMMENT

While the usefulness of routine serum surveys of this kind can be established only through prolonged experience, the simplicity of the plan recommends it. The specimens required are constantly available without additional effort. Furthermore the pools can be held for further testing at a later date and may have as much future as present value. Collections of this kind have several times proven of considerable value to us. The size of the samples will doubtless need to be adapted to the problem at hand and it is probable that more precise selection of specimens according to a sound plan will become desirable in the case of influenza. What factors may be of greatest

importance in assembling the samples remain to be determined.

The differences in results obtained by the two methods of testing raise the question of their relative value for studies of this kind. Although the technic of the complement-fixation test used in these studies apparently indicated a sharper differentiation between acute- and convalescent-phase sera, there was close agreement between the two methods. The reasons for the divergencies noted in the results with the pooled sera are, no doubt, multiple. The dilution as a result of pooling and the relative sensitivity of the tests may be factors. The complex character of influenza antigens and antibodies must also be considered. Suffice it to say at this time that experimental evidence at hand makes it seem worth while to continue the study with the complement-fixation method.

CONCLUSIONS

The routine testing of serum pools may be of value as a public health laboratory procedure and may supply data useful in estimating the prevalence, distribution and susceptibility to certain diseases.

Pools from all parts of New York State exclusive of New York City have been periodically tested for influenza antibody titers.

The results suggest that influenza-A antibodies were relatively high in the summer of 1945 but steadily diminished thereafter. Influenza-B antibodies were relatively low in 1945 but increased in some areas following the epidemic of December, 1945.

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Rheumatoid Arthritis*

The Diagnostic Significance of Focal Cellular Accumulations in the Skeletal Muscles

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THE diagnosis of typical, far advanced rheumatoid arthritis is not a difficult problem. However, the differentiation of this disease in its early and atypical forms from gout, osteoarthritis, infectional arthritis, rheumatic fever, and the "erythema group" first mentioned by Osler[1] is often a matter of conjecture. To confuse the differential diagnosis still further, there are such ill defined syndromes as fibrositis, palindromic rheumatism, Reiter's syndrome and what is sometimes referred to as "psychogenic rheumatism." Some of these patients, in particular those with fibrositis and palindromic rheumatism, may indeed be in the initial stages of rheumatoid arthritis.[2] The diagnosis of many of these conditions is based on the clinical picture and history alone, while in some there are laboratory procedures such as cultures, roentgenograms, agglutination studies and sedimentation rates to aid in the diagnosis. These, however, are often normal or equivocal.

The work of Freund[3] and his collaborators, therefore, is of particular interest. In 1945, they described the presence of clusters of lymphocytes, plasma cells and epithelioid cells among the muscle fibers of the amputated legs of a patient with rheumatoid arthritis. In addition to these accumulations of cells, they noted definite changes in the muscle cells, consisting of hydropic degeneration, edema, loss of striation, marked swelling and atrophy of muscle fibers. They were able to demonstrate these same changes in muscle biopsies obtained in fourteen other cases of rheumatoid arthritis. In a control study, no such lesions were found, and the authors came to the conclusion that these pathological findings in rheumatoid arthritis were specific. The same results were reported in an additional paper by Steiner, Freund, Leichentritt and Maun.[4] It was concluded here that the cellular accumulations in the endomysium occurred in the early stage of the disease and preceded the degenerative changes in the muscle fibers. Similar cellular infiltrations of the perineural and periadventitial perimysium were also found in later stages of the disease.

During the past year an effort has been made to confirm the findings of Freund and his collaborators, and further to ascertain whether muscle biopsy could aid when the diagnosis was obscure. Dawson[5] believed that there was little justification for separating rheumatoid arthritis in which "atrophic" changes predominated from "non-specific infectious" arthritis. He pointed out that a similar course, similar roentgenograms, agglutinins for hemolytic streptococci and subcutaneous nodules occur in both. In this study these groups have been separated for the sake of analysis.

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MATERIAL

The patients studied were from the Arthritis Clinic, the Orthopedic Clinic and the Medical and Pediatric wards of the New Haven Hospital. Biopsies were taken arbitrarily from the bellies of the deltoid and the gastrocnemius muscles. With the aid of ½ per cent novocaine, blocks of muscle tissue 1 cm. in greatest diameter were removed.

In all, biopsies were performed on thirty-one patients. Sixteen of the thirty-one biopsies were from clinically typical rheumatoid arthritis of the "atrophic" type. Eight of the sixteen were males and eight were females. The duration of disease in the group was two to eighteen years. With the exception of two, all were in the active phase of the disease as judged by clinical pictures and sedimentation rates. There was roentgenographic evidence of osteoporosis and narrowing of the joint spaces in each case, and nine of the sixteen patients had been given gold therapy prior to the time the biopsy was done.

The other fifteen were included in the study either as controls or because the diagnosis was obscure. Among the nine controls there were two cases of rheumatic fever, and one case each of osteoarthritis, hypochondriasis and gonococcal arthritis, and four cases of "non-specific infectious" arthritis. Further controls were obtained from twenty-three autopsies in whom no rheumatoid arthritis was present. These autopsy controls were selected only on the basis of being within the same age range as our cases of rheumatoid arthritis. The group included three patients with generalized arteriosclerosis, two with tuberculosis, three with rheumatic fever, one traumatic death, two suicides and one each with carcinoma of the lung, carcinoma of the lip, Hodgkin's disease, liver abscess, glomerulonephritis, fatty liver, subacute bacterial endocarditis, dissecting aneurysm, diabetes mellitus, duodenal ulcer, Guillain-Barré's syndrome and cerebellar glioma.

RESULTS

All of the pathological findings both of the rheumatoid arthritis cases and the controls are included in Table 1.

The biopsies of thirteen of the sixteen cases with rheumatoid arthritis showed focal

TABLE 1
INCIDENCE OF LESIONS IN PATIENTS WITH ARTHRITIS OF VARIOUS TYPES AND ALSO IN AUTOPSY CONTROL GROUP

	No. of Patients	Cellular Foci		Muscle Fiber Changes*
		Perivascular in perimysium	Endomysial	
Rheumatoid Arthritis	5	+	+	+
	5	+	−	−
	3	−	−	−
	2	+	−	+
	1	−	+	+
	Total 16			
"Non-specific Infectious" Arthritis	1	+	+	−
	1	−	+	+
	1	−	−	+
	1	−	−	−
	Total 4			
Osteoarthritis	2	−	−	−
	1	+	+	+
	1	−	−	+
	Total 4			
Gonococcal Arthritis	1	−	−	−
	Total 1			
Rheumatic Fever	4	−	−	−
	1	−	−	+
	Total 5			
Autopsy Cases	11	−	−	−
	6	−	−	+
	Total 17			

* Including increased eosinophilic staining, loss of definition of myofibrils and striations, vacuolization, atrophy and proliferation of fibroblasts in endomysium.

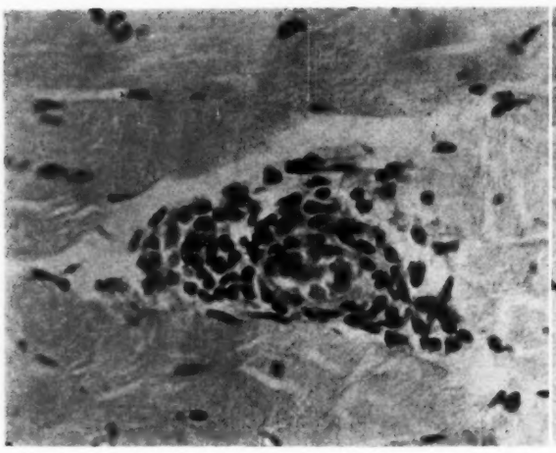

FIG. 1. Perivascular focal cellular accumulation. Case No. 26; hematoxylin eosin. 580 X.

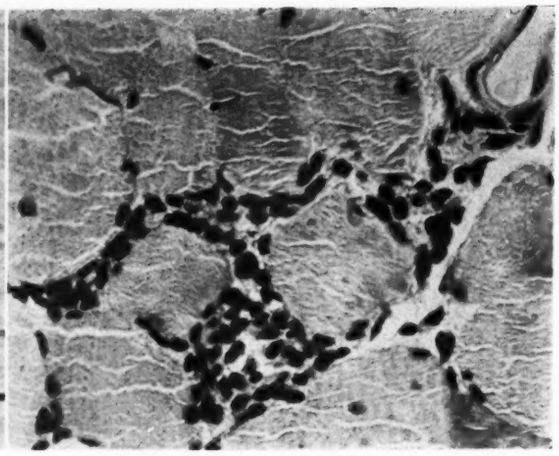

FIG. 2. Cellular accumulations in endomysium surrounding uninvolved muscle fibers. Case No. 26; hematoxylin eosin. 580 X.

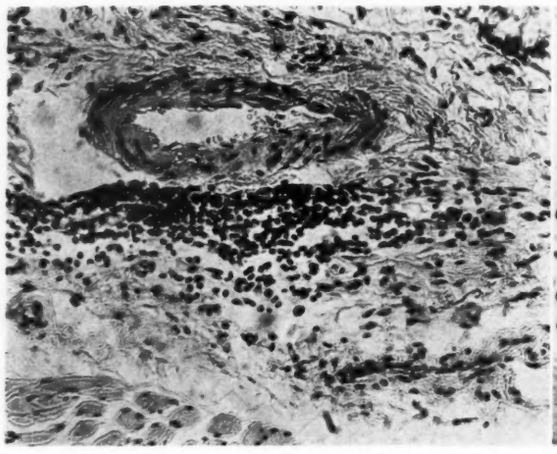

FIG. 3. A focal accumulation of cells in perimysium adjacent to an arteriole. Case 19; hematoxylin eosin. 270 X.

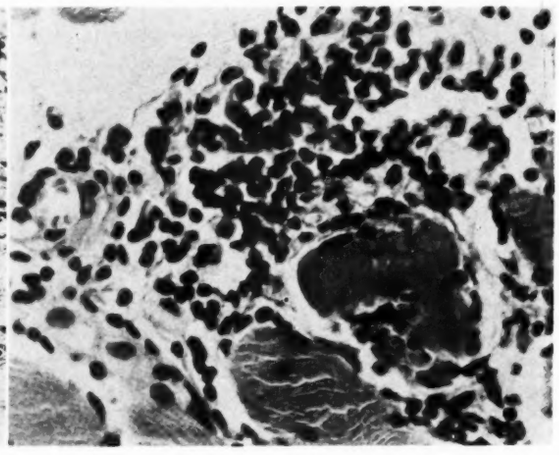

FIG. 4. Focal cellular accumulation in perimysium in proximity to hyaline degenerating muscle fiber. Case 13; hematoxylin eosin. 580 X.

cellular accumulations. These consisted of collections of lymphocytes, with fewer macrophages and rarely scattered plasma cells and eosinophiles; they were most commonly located perivascularly in the perimysium and less frequently in the endomysium between the individual muscle fibers. The perimysial foci were not related to the small nerve branches nor were changes noted in the walls of the small arteries or veins lying in juxtaposition to the foci. (Figs. 1, 2 and 3.) Changes found in the muscle fibers were interpreted as degenerative. These included increased eosinophilic staining, loss of definition of the myofibrils and striations, vacuolization and atrophy. Fibroblasts were increased in number but there was no conspicuous fibrosis. (Fig. 4.) These muscle changes were in most instances, though not always, accompanied by cellular foci in the endomysium; the latter were also at times unassociated with muscle fiber degeneration. Necrotic foci, conspicuous accumulation of polymorphonuclear leukocytes and bacteria could not be found.

There seemed to be no correlation between the presence of a positive biopsy and the duration of the illness. The lesions found

in patients with old, inactive disease did not differ in character or extent from those found in active cases, nor did there seem to be any relation between the presence of these muscle changes and gold therapy. The presence of a positive biopsy could not be correlated with the degree of atrophy of the muscle biopsied.

With the exception of one patient who may have had lupus erythematosis disseminatus, there were no clinical features to distinguish the three cases of rheumatoid arthritis with negative biopsies from those with positive biopsies. Two of the three had Marie-Strümpell arthritis as well as disease of their peripheral joints.

It was of interest to find that two of four patients with "non-specific infectious" arthritis showed the same cellular foci as those found in the cases of rheumatoid arthritis.

Muscle was studied from one patient with clinical osteoarthritis and from three autopsies in which the diagnosis of osteoarthritis had been made as an incidental finding in routine *x*-rays. The biopsy from the clinical case showed changes indistinguishable from those in the rheumatoid arthritis group. This patient gave a history of having had twenty years previously, a three-month febrile illness associated with polyarthritis. The sections from the autopsied cases showed no cellular foci, but in one of the three there were hyalin degenerated muscle fibers.

Muscle from five patients with acute rheumatic fever has been studied. Two were clinical cases and three were taken from the autopsy material. No cellular foci as observed in the rheumatoid group were found. Hyalinization and vacuolization of the fibers, however, were present in one. No lesions were found in the muscles of the remaining seventeen autopsy controls.

The six cases included in the study who were diagnostic problems were of particular interest. The differential diagnosis in each case rested between rheumatoid and some other form of arthritis. In only one was the biopsy positive. This patient subsequently developed fairly typical rheumatoid arthritis although her *x*-rays are still negative. The remaining five patients, whose biopsies were negative, continue to be diagnostic problems.

COMMENT

Not all cases of rheumatoid arthritis have yielded positive biopsies, yet in these studies the cellular foci in the muscles were found only in cases that were clinically classified as rheumatoid arthritis and "non-specific infectious" arthritis, with the exception of one patient with clinical osteoarthritis who gave a history suggestive of old rheumatoid arthritis. These findings would give no indication of any fundamental difference between the "atrophic" and "non-specific infectious" forms of rheumatoid arthritis.

How early in the course of the disease these inflammatory foci appear is not known, but that they can appear before *x*-ray evidence of joint disease is manifest is shown by the one case in the group presenting a diagnostic problem in which a positive biopsy was obtained before *x*-ray changes were present in the joints. The nature of the focal lesions is unknown. Pathologically, they consist of collections of cells of the type seen in chronic inflammatory foci, most commonly in perivascular locations, but also in the endomysium between the individual muscle fibers. Lesions of the adjacent vessels were not found nor were the foci related to the nerve fibers. There was no necrosis found in association with the perimysial foci. No other stage of the process was detectable; the appearance was always essentially the same. Fibrosis was insignificant.

Changes in the muscle fibers, at times definitely degenerative in type, were fairly frequent. Such fibers were often but not

always surrounded by cellular accumulations. The pathogenesis of hyalinization and loss of definition of myofibrils and their striations is not known. This alteration was also found in some of the control series. It may be related to their terminal illness but certainly is not peculiar to rheumatoid or "non-specific infectious" arthritis.

The presence of these skeletal muscle changes along with subcutaneous nodules and the findings of endocardial and myocardial lesions reported by Baggenstoss and Rosenberg[6] and by Bayles[7] is further evidence that rheumatoid arthritis is a systemic disease. The fact that such lesions were not found in our rheumatic fever controls is of interest in relation to the discussion concerning the relationship of rheumatoid arthritis and rheumatic fever.

SUMMARY

Muscle biopsies were obtained in sixteen cases of rheumatoid arthritis in an effort to repeat the work of Freund[3] and his collaborators. As controls, biopsies were obtained in fifteen other patients among whom were included cases of osteoarthritis, rheumatic fever, gonococcal arthritis, and "non-specific infectious" arthritis; similar studies were made in twenty-three routine autopsy cases.

Muscle lesions were found in thirteen of the sixteen cases of rheumatoid arthritis and in two of the four control cases of "non-specific infectious" arthritis. With the exception of one patient with osteoarthritis who had a history suggestive of rheumatoid arthritis these lesions were absent from all other controls. Our results would give no indication of any fundamental difference between the "atrophic" and the "non-specific infectious" forms of rheumatoid arthritis.

The lesions consisted of focal accumulations of lymphocytes and macrophages and occasional plasma cells and eosinophils occurring either in perivascular locations in the perimysium or in the endomysium between the individual muscle fibers. Hyalinization, vacuolization, loss of striations and atrophy of muscle fibers were found frequently in association with these cellular foci in the above group, while in the controls similar degenerative changes occurred without any cellular reaction.

These cellular accumulations would appear to be further evidence of the systemic nature of rheumatoid arthritis. Although they have not been found in all cases of this disease, their presence has been limited almost exclusively to rheumatoid arthritis. Their nature is unknown, and their direct relationship to the duration or activity of the disease is as yet undetermined.

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Reviews

The Diagnosis of Guillain-Barré's Disease

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WITHIN recent years there has appeared an increasing interest in the symptom complex known as Guillain-Barré's disease. Actually, this illness has been recognized since 1892 when Osler[1] first described it under the term of "acute febrile polyneuritis." However, since that time it apparently has been lost in the maze of specialized literature and has been revived periodically under different titles (radiculoneuritis—Guillain, Barré, and Strohl;[2] acute ascending paralysis—Casamajor;[3] acute infective polyneuritis—Bradford, Balford, and Wilson;[4] infective neuronitis—Kennedy;[5] polyneuritis with facial diplegia—Francois, Zuccole, and Montus[6] and Taylor and McDonald;[7] myeloradiculoneuritis—Shaskan, Teitlebaum, and Stevenson;[8] encephalo-myelo-radiculitis—Polan and Baker,[9] etc. Currently this illness has become widely accepted as Guillain-Barré's disease since these investigators first emphasized one of the most characterizing features of the illness, namely, a low spinal fluid cell count associated with an elevated protein. Actually these investigators reported twelve cases, all of whom developed a flaccid paralysis of the limbs with some involvement of both deep and superficial sensation. All their cases showed an increased spinal fluid protein of 1 to 2 Gm. and all recovered without residuals. Although this illness is known as Guillain-Barré's disease, the original criteria described and insisted upon by these investigators are no longer adhered to. Careful and detailed study of large groups of patients has revealed many variations of this symptom complex and has suggested that this illness has the capability of implicating any part of the nervous system, thus producing a variable symptomatology. It is because of the kaleidoscopic picture often presented that the actual diagnosis, particularly in the acute phases, is often fraught with dangers and inaccuracies. It is with the hope of at least pointing out some of the variations in this illness and the possible errors in diagnosis that the present review is undertaken.

It must be realized at the onset that there is no single clinical finding or laboratory test that enables one to make a diagnosis of Guillain-Barré's disease. In view of the absence of any specific etiological agent we are forced to accept a more practical attitude and to consider in the diagnosis all the features presented. It is only after a careful consideration of all the symptoms and signs that one can arrive at a final satisfactory diagnosis. This frequently will necessitate a fairly prolonged period of observation before one feels justified in classifying the illness and venturing a diagnosis.

Before pointing out the numerous pitfalls in the diagnosis of this illness, it might be well to recapitulate certain of the characterizing features. It is obvious that without a thorough knowledge of this illness, one cannot hope to avoid errors in diagnosis.

1. *A Rather Sudden Onset Occasionally Preceded by a History of Some Antecedent Infection,*

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Chiefly of the Respiratory Tract. Premonitory symptoms may vary from such mild complaints of malaise, backache, muscle and joint pain, mild lethargy to such acute disturbances as vertigo, severe radicular pain, headaches, acute muscle tenderness and anorexia. In many cases the illness is very slow in onset, gradually progressing over a period of months before the full-blown syndrome becomes apparent.

2. *Radicular Involvement.* This is one of the most constant features of the illness. The radicular pain is early in onset, involving chiefly the extremities. Pains may be widespread and difficult to control.

3. *Severe Muscle Tenderness.* Muscle tenderness occurs early and may persist even during recovery. Tenderness is so acute that it is precipitated by the slightest pressure.

4. *Triceps Weakness.* Regardless of the regions of the body predominantly involved by the disease, the triceps muscles seem to be implicated, resulting in severe triceps weakness even in the presence of otherwise intact muscles of the upper limbs.

5. *Facial Nerve Palsy.* Involvement of the seventh cranial nerve is present in about 30 per cent of the cases. This disturbance may be bilateral or unilateral, the latter appearing as a Bell's palsy.

6. *Absence of Those Findings Suggestive of a Septic or Toxic Reaction in Spite of the Severe Clinical Symptomatology.* The patients generally show no hyperpyrexia, leukocytosis or increased sedimentation rate. Whenever the laboratory findings indicate definite variations from normal, one must check carefully for some complicating infection.

7. *A Cell-protein Dissociation in the Spinal Fluid with a Normal Cell Count and a High Protein.* This finding even in a large series is present only in from 60 to 80 per cent of the cases. Many investigators have placed too much emphasis upon this single laboratory finding. It alone is neither pathognomonic nor absolutely necessary for a diagnosis of this disease. It is the dependence upon this single feature that has led to many erroneous diagnoses.

8. *Sensory Involvement.* Sensory involvement of some type associated with the motor complications is by no means constant but extremely helpful in the diagnosis. Paresthesias, hyperesthesias and anesthesias may occur. The sensory disturbances may follow a peripheral, radicular or segmental distribution.

9. *Marked Hyperirritability Often with Definite Personality Changes.* These patients often become irritable, restless and difficult to please. They tend to change from calm, composed and pleasant individuals to cantankerous, difficult patients. Definite mental symptoms are usually absent although somnolence and mild lethargy are by no means uncommon.

10. *Favorable Prognosis Usually with Fairly Good Functional Recovery.* Generally one can say that recovery is the rule regardless of the severity of the clinical picture. However, in the more severe cases fatalities do result with an over-all mortality rate of 10 per cent increasing to as high as 40 per cent in individuals over fifty years of age. Residuals may occur in the more severe cases.

Guillain-Barré's disease may affect any part of the nervous system, but the involvement tends to be accentuated in certain regions. For convenience the disease has been classified into five clinical forms, depending upon the region most severely implicated, namely, the abortive or mononeuritic form, the polyneuritic form, the myelitic form, the bulbar form and the encephalitic form. Each of these types will show scattered symptoms and findings of involvement of other regions and all have in common the characteristic clinical features of the disease described above. The pitfalls encountered in diagnosing this illness will be discussed in relationship to each of

these five clinical forms of the disease. In the illustrative cases presented in this paper the diagnosis of Guillain-Barré's disease was either made or strongly suggested by the clinical picture, but was subsequently found to be untenable and had to be abandoned in light of subsequent developments.

ABORTIVE OR MONONEURITIC FORM

Patients with this form of the disease complain of fleeting pains with associated muscle aching and weakness largely limited to one limb or one nerve distribution. Occasionally more than one nerve or muscle group may be involved giving the picture of multiple mononeuritis. Despite the fact that the symptoms are predominantly mononeuritic there are also scattered findings of mild weakness, reflex changes or sensory impairment which indicate a more diffuse involvement. These scattered findings may be overlooked if a careful search is not made.

The differential diagnosis includes any disorder which produces an acute mononeuritis or multiple mononeuritis (trauma, alcohol, lead, arsenic, infections, diabetes, vitamin deficiencies, etc.). A careful history of the onset of the palsy may help. Pressure palsies usually come on rather abruptly with the history of pressure on the nerve at a vulnerable spot. Generally the absence of any associated scattered neurological findings speaks against a diagnosis of Guillain-Barré's disease. A spinal cord tumor or a protruded intervertebral disc may present a difficult differential diagnosis until the passage of time establishes the correct diagnosis. As a rule, while on strict bed rest, cases of Guillain-Barré's syndrome improve while the symptoms in a cord tumor tend to be progressive.

Metastatic malignancy may simulate Guillain-Barré's disease for a considerable period. In metastatic involvement the pain is usually much more intense and persistent, the course is progressively downhill and symptoms referable to other organs are often present. In a metastatic lesion the spinal fluid protein may be much higher than in Guillain-Barré's disease, often reaching as high as 1 to 2 Gm. per cent. One is most often lead astray when circumstances prevent one from obtaining an adequate history of the onset of the patient's symptoms.

Certain systemic diseases may be mistaken for the mononeuritic form of Guillain-Barré's disease. These diseases have in common a scattered and sometimes widespread involvement of the nervous system as a part of the pathologic process which implicates many organs of the body. The nervous system damage is usually secondary to the vascular, inflammatory or invasive lesions characteristic of the disease. Multiple mononeuritis, for example, is the most common neurologic complication of periarteritis nodosa and is one of the most frequent of all the symptoms of this disease. Boeck's sarcoid, dermatomyositis and metastatic malignancy may closely mimic Guillain-Barré's disease. We have recently seen a case of lupus erythematosus with widespread neuritic findings. With the exception of dermatomyositis, any of these diseases may produce encephalitic, bulbar or myelitic syndromes but most commonly produce the poly- or mononeuritic forms. The differentiation is made on the presence of some of the following findings, none of which is seen in Guillain-Barré's disease: anemia, eosinophilia, albuminuria, hematuria, skin lesions, cardiac symptoms, pulmonary findings, evidence of disease of other organs and generally a downhill course with or without remissions and exacerbations. Cell-protein dissociation may also occur in any of these systemic illnesses and cannot be used as a differentiating finding. It may be necessary to follow the course of the patient's illness over a period of time before the correct

diagnosis can be established. The following is a case illustrating this point.

CASE 1. J. G. Fifty-three year old farmer, was admitted to the hospital in April, 1946, with complaints of weakness of the extremities and pains in the chest. He considered himself to be in good health until October 11, 1945, at which time he developed a severe pain over the precordium. The patient was hospitalized for ten weeks and was treated with oxygen. While in the hospital he developed herpes zoster of the left supraorbital area and on the inner aspect of the right thigh. Following this he noted numbness and weakness of the arms and legs. These symptoms increased after discharge from the hospital, and the patient was found to have a generalized flaccid paralysis. Routine blood studies and urinalysis were normal. Spinal fluid was negative. Urine examinations for lead, arsenic and porphyrins were negative. The patient improved under physical therapy and was discharged with a diagnosis of Guillain-Barré's disease.

Two weeks before his present admission he developed a recurrence of the chest pain and the numbness and weakness of his hands and feet. He also had complaints of shortness of breath, non-productve cough, weight loss and loss of appetite. Physical examination revealed a middle-aged man who appeared chronically ill. He had scars of the old herpes zoster. The left pupil was fixed to light. Neurologic examination revealed diminution to loss of all modalities of sensation in the arms and legs. This was of a glove and stocking distribution and was more intense peripherally. There was a grade 1 to grade 2 weakness of the muscles of the extremities more marked peripherally. Tendon reflexes were markedly diminished in the arms and absent in the legs. There was a slight right facial weakness.

Blood studies now showed an anemia with a hemoglobin of 8.9 Gm., red cell count of 2,750,000 and leukocyte count of 8,000 and 13,400 on different occasions. Differential smear revealed fifty neutrophiles, forty lymphocytes, one monocyte and nine eosinophiles. Urinalysis was repeatedly negative. Spinal fluid showed a negative reaction and the spinal fluid protein was 48.5. Thoracentesis produced blood tinged fluid with 3,500 leukocytes of which 85 per cent were neutrophiles. Culture of this fluid was negative.

While in the hospital the patient's symptoms subsided, and he was returned home improved. Diagnosis was made clinically of periarteritis nodosa. Because of the anemia, general appearance of toxicity, cardiac symptoms, pulmonary findings, and recurrent nature of the illness the diagnosis of Guillain-Barré's disease was no longer tenable. A clinical diagnosis of periarteritis nodosa seemed warranted on the basis of the findings noted above. Early in the course of this patient's disease the findings suggested a mononeuritic form and later the picture resembled that of the polyneuritic form of Guillain-Barré's disease.

Poliomyelitis characteristically attacks scattered and isolated muscle groups and may be difficult to differentiate from Guillain-Barré's disease. This is especially true if the poliomyelitis presents itself with little fever and minimal meningeal irritation, or if the case occurs out of the usual poliomyelitis season. More commonly, however, the reverse occurs and cases of Guillain-Barré's disease are classified as atypical poliomyelitis. Usually in the latter the course is more febrile, there is more meningeal involvement, there are more cells in the spinal fluid and the involvement is predominantly of a lower motor neuron type showing no spasticity or sensory disturbances.

POLYNEURITIC FORM

This form is the most commonly recognized clinical type. Usually ushered in by premonitory symptoms, there is the gradual or sudden development of a flaccid paresis which generally involves the lower extremities earlier and to a greater extent than the upper limbs. The weakness is usually symmetrical and somewhat more severe in the proximal muscles. The disorder seems to have a predilection for the triceps, deltoids and extensors of wrist and fingers while the psoas, hamstrings and

peroneals are more severely involved in the lower extremities. Facial palsies are common. The musculature of the chest and abdomen becomes implicated in the severe cases. Paraesthesias, hyperaesthesias and pains are common but sensory loss is less prominent than the motor involvement. Diminution of vibratory and joint sensibility is more common than decreased superficial sensation.

Peripheral neuritis of an infectious or toxic type may be confused with Guillain-Barré's disease. Usually the former occurs in the course of some febrile illness, is distal in its distribution and remains localized to the limbs. Cranial nerve involvement is rare. Cell protein dissociation may occur.

Neuritis due to alcoholism, vitamin deficiency or diabetes should be excluded on the basis of history, examination and laboratory findings. Lead neuropathy should be considered, but the presence of lead in the urine may be misleading because painters and gardeners are in no way protected against true Guillain-Barré's disease or periarteritis nodosa. History of exposure or lead in the urine is not necessarily sufficient to establish it as the etiology of neurologic symptoms.

Post-diphtheritic paralysis may give a clinical picture which is indistinguishable from Guillain-Barré's disease. We have recently seen four patients in whom this was true. Malaria may be followed by the neurologic findings of Guillain-Barré's disease, a long recognized fact which gains new significance when evaluating neuropathies in World War II veterans. Poliomyelitis, periarteritis nodosa, disseminated lupus erythematosus and Boeck's sarcord may resemble the polyneuritic form but have been described above.

The neurologic manifestations of acute porphyria may be identical with those of Guillain-Barré's disease. This similarity may even include cell-protein dissociation. Mental symptoms often suggest an encephalitic form of Guillain-Barré's disease. There is usually a history of gastrointestinal symptoms, and there may be a change in the color of the urine. The differentiation is important because of the tendency to recurrence and the poor prognosis in acute porphyria. Gastrointestinal symptoms, recurrent paresis, mental change, and dark urine should make one alert to the possibility of an acute porphyria. The following case is presented in brief to illustrate this point:

Case II. J. C., white male, was examined on neurologic consultation in April, 1946, with the complaints of weakness of the arms. He gave a history of the onset of abdominal pains about October 20, 1945. About November 1, 1945, the patient noted aching of his arms, back and legs. This progressed and about Christmas he complained of weakness of his arms and felt that his legs would "give out" at times. Neurologic examination revealed decreased to absent tendon reflexes in the arms with normal tendon reflexes in the legs. Strength in the right arm was normal to −2 and in the left arm −1 to −3. There was a paresis of the biceps, supinators, pronators and extensors of wrists and fingers. There was slight weakness of the right psoas and of the flexors and extensors of the toes bilaterally. Sensation was intact.

Routine urinalysis and blood count were normal. Blood non-protein nitrogen was not done. There were large amounts of porphobilinogen and uroporphyrin in the urine on qualitative tests, and a diagnosis of acute intermittent porphyria was established. Spinal fluid examination was requested but was not performed. The patient was discharged improved. He returned to the hospital August 11, 1946, with a recurrence of severe abdominal pain and died suddenly and unexpectedly two days later.

In this patient the diagnosis of acute porphyria had been established before the neurologic consultation was requested. However, other cases with less obvious gastrointestinal complaints will present greater difficulties in differential diagnosis. Any patient with symptoms of Guillain-Barré's disease who develops gastrointestinal symptoms or recurrent neurologic symptoms should be investigated for porphyria.

MYELITIC FORM

Myelitic involvement in Guillain-Barré's disease is common and may be found in almost one-half of the cases. (Minimal pyramidal tract findings may be missed unless searched for.) The myelitic symptoms tend to come on rapidly with numbness and weakness beginning in the lower extremities. The motor involvement may be entirely flaccid or largely flaccid with some spastic elements. The tendon reflexes are usually reduced but may be hyperactive. Segmental sensory loss with a definite level is often seen. Bowel and bladder dysfunction occur early. There is usually rapid recovery with relatively little residual when compared with the severity of the symptoms at their peak.

This condition must be differentiated from the infectious myelitis occurring during the course of some febrile diseases. In the latter the onset is generally slower, the peak is reached later, the patient appears toxic and there are often severe residuals. The spinal fluid protein is usually accompanied by an elevated cell count. A vascular (thrombotic) myelitis tends to be abrupt in its onset.

The first attack of multiple sclerosis may be very difficult to distinguish from the myelitic form of Guillain-Barré's disease. The patient may relate his attack of multiple sclerosis to an antecedent upper respiratory infection. In both diseases there is a marked tendency to spontaneous recovery. The spinal fluid protein may be elevated mildly in some patients. However, Guillain-Barré's disease seldom tends to recur and following the doubtful case over a period of time should establish the correct diagnosis.

Psychoneurosis at times may simulate the myelitic or polyneuritic form of the disease. These patients may come in complaining of weakness and pains. The pains may be in the trunk or extremities and bear a resemblance to radicular pains. There may be hyperaesthesias and complaints of muscle tenderness. The patient's emotional instability often simulates the irritability and personality changes seen with Guillain-Barré's disease. Careful muscle testing should reveal the weakness to be more apparent than real. The reflexes are generally hyperactive in contrast to the usual diminished reflexes in Guillain-Barré's disease. Sensory examination is normal or bizarre. Spinal fluid findings are normal. Careful neurologic and psychiatric history and examination should establish the correct diagnosis. Occasionally one may have to resort to observing the patient over a period of time and to electrical testing of paretic muscles for confirmation of the clinical impression. The following case is presented in brief to illustrate this problem:

CASE III. R. C., a twenty-one year old male, was admitted to the hospital with complaints of weakness and nervousness. He gave a history of having had pneumonia three weeks previously for which he was given penicillin and sulfadiazine. During his convalescence he noted weakness, aching of the legs, and pain in the chest. He further gave a history of nervousness of several years' duration, fear of closed places, palpitation and tremor. He had been discharged from the army because of nervousness and the patient considered that he had too many illnesses to work.

Neurologic examination revealed generalized hyperactive reflexes. There was apparent generalized weakness, but careful testing failed to detect any actual weakness of any of the muscles tested. Spinal fluid examination was negative except for the total protein which was reported as 71.5 mg. per cent. Neurologic consultation failed to show any evidence of neurologic disease. An investigation revealed that due to technical error all of the spinal fluids done at that time had been reported with elevated protein levels. The erroneous report of elevated spinal fluid protein was misleading in suggesting the diagnosis of Guillain-Barré's disease.

BULBAR FORM

Generally this type of the illness is accompanied by involvement of other parts of the nervous system, even though the bulbar symptoms do comprise the most impressive part of the clinical syndrome. Any of the cranial nerves may be implicated resulting in ophthalmoplegias, diplopia, facial anesthesia, facial palsies, dysarthria, dysphagia, etc. The latter three disturbances are by far the most frequent. In most cases there is an associated involvement of the limbs with motor or sensory disturbances. In spite of the apparently severe involvement in such a vital region the prognosis is usually good, particularly in individuals under fifty years of age. The diagnosis is generally suspected because of the afebrile course, the early facial palsy, the associated radicular involvement of the limbs and the cell-protein dissociations in the spinal fluid.

This form of the illness must be differentiated from any condition producing a bulbar palsy. Probably the most difficulty arises in its differentiation from the bulbar type of poliomyelitis. This is extremely important since the latter often carries with it a much poorer prognosis. In poliomyelitis there is usually a febrile course, signs of meningeal involvement, increase of cells in the spinal fluid and a seasonal occurrence, often with other cases in the region.

The bulbar involvement in progressive muscular atrophy, amyotrophic lateral sclerosis, arteriosclerosis, pseudobulbar palsy, causes no real diagnostic difficulties since the onset is very slow and the course generally chronic. The facial nerve is generally spared and the spinal fluid remains unchanged.

CEREBRAL FORM

This is an extremely rare and not usually recognized type of Guillain-Barré's disease. It often begins with severe headaches, malaise, vertigo and nausea. The symptoms may subside only to be followed by facial weakness or scattered paresis or radicular pain. After a few days the headaches again return and are accompanied by lethargy, confusion or restlessness. Papilledema is often present. The prognosis is guarded, although many patients make a fairly complete recovery.

By far the most difficult problem in these cases is their differentiation from cerebral neoplasms. Frequently the associated motor involvement suggests the focal lesions seen in brain tumors. In the presence of such a clinical picture one is often forced to resort to air studies in order to eliminate the possibility of a brain tumor. In many cases, however, careful attention to the symptomatology will suggest the proper diagnosis. In Guillain-Barré's disease the neurological findings are often scattered and accompanied by severe radicular pain. In spite of a papilledema the spinal fluid pressure is usually not greatly elevated but the protein is definitely increased.

Multiple sclerosis may also cause considerable diagnostic difficulty particularly since papillitis may also occur in this illness. A careful survey of the history, the more chronic and remitting course, the first zone colloidal gold curve, etc., all are aids in the proper evaluation of the patient.

COMMENTS

Obviously in a brief discussion it is impossible to include all of the difficulties encountered in arriving at an accurate diagnosis of Guillain-Barré's disease. At most one can only hope to point out some of the more common diagnostic problems. With the increasing frequency with which this diagnosis is made, it becomes of extreme importance to caution against too hasty an acceptance of such a diagnosis. This is particularly true since so many illnesses, often with an entirely different

course and prognosis, may simulate the clinical picture seen in Guillain-Barré's disease.

Before completing these comments it might be well to list a group of findings which rarely occur in Guillain-Barré's disease and which, if present, should caution against such a diagnosis until careful and detailed history and investigation have eliminated every other diagnostic possibility. Even after such a study it may still be necessary to withhold a final diagnosis until the patient has been observed over a considerable period of time.

1. *Recurrences.* In most cases, usually after an acute onset, this illness becomes stationary or starts to subside. It appears that improvement, once begun, continues uninterrupted, provided moderate care and rest are obtained. Repeated relapses should make one uneasy about the accuracy of the diagnosis.

2. *Symptoms of Involvement of Other Organs.* Although systemic involvement has been described in this illness, the nervous system presents the predominant and often exclusive clinical symptomatology. Clinical evidence of involvement of other organs of the body is extremely rare in Guillain-Barré's disease.

3. *Toxicity and Fever.* The patients with Guillain-Barré's disease show almost no hyperpyrexia or signs of toxicity. In the absence of some complicating infection in the urinary or respiratory tract, such findings generally speak against a diagnosis of this illness.

4. *Protein of 1 Gm. or More.* Although Guillain, Barré and Strohl insisted on the presence of 1 to 2 Gm. of protein in the spinal fluid before justifying a diagnosis of this illness, it has been our experience that such a large amount of spinal fluid protein is extremely uncommon and when present generally suggests some other condition. Very few patients with Guillain-Barré's disease will show a protein elevation beyond 300 to 400 mg. per cent.

5. *Meningeal Symptoms.* Signs of meningeal irritation, that is, headache, stiff neck and backache have been reported in scattered cases of Guillain-Barré's disease. In our experience this is an extremely uncommon finding and, therefore, should not be used diagnostically.

6. *Eosinophilia, Anemia, Hematuria, Albuminuria.* These findings generally suggest some systemic process with an involvement that is more widespread than the nervous system alone. Any of these findings should caution one against a diagnosis of Guillain-Barré's disease and should stimulate one to intensify his search for other etiological factors in the illness.

7. *Downhill Course.* Although the occasional patient with Guillain-Barré's disease will fail to improve, recovery is the rule in spite of the severity of the clinical picture. For this reason when a patient fails to respond, one must make a diagnosis of this illness with great caution.

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Agranulocytosis Caused by Thiouracil*

A Review of Fifty-nine Cases in the Literature and a Report of Two Additional Cases

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THE introduction of thiouracil as an effective agent in the treatment of thyrotoxicosis has resulted in an increasing incidence of toxic reactions following the continued use of the drug. Of the reactions thus far observed by far the most serious has been the development of agranulocytosis. The application of the term, agranulocytosis, has varied considerably. Its use should be properly restricted to patients whose leukopenia is very severe and is associated with an extreme reduction or complete absence of granulocytes and whose clinical picture is usually characterized by evidence of fever, toxicity and necrotic lesions especially of the mouth and throat.

The incidence of agranulocytosis in patients treated with thiouracil averages about 1.88 per cent. (Table I.) In a report from 328 investigators,[1] the incidence of granulocytopenia in 5,745 patients treated with thiouracil was 168 or 2.5 per cent. This number, however, included atypical cases of simple leukopenia with neutropenia. Tyson, Vogel and Rosenthal[2] reported six cases of severe agranulocytosis in a small series of fifty-four cases, an unusually high incidence (11 per cent) that they could not satisfactorily explain. Of 1,091 thiouracil cases compiled from the reports of twelve clinics[3] there were nineteen cases of agranulocytosis, an incidence of 1.74 per cent.

In the majority of cases, agranulocytosis occurs during the second month of treatment with thiouracil. Moore[3] found this to be true in 79 per cent of his nineteen collected cases. (Table I.) In twelve of the sixty-one cases reported to date (Table II), the duration of thiouracil therapy was not stated. Of the remaining forty-nine patients, thirty-one or 63 per cent developed the condition during the second month of treatment; five or 10 per cent during the first month; six or 12 per cent during the third month; and seven or 14 per cent after that time. The shortest interval between the beginning of thiouracil therapy and the onset of symptoms was one or two weeks

TABLE I
INCIDENCE OF AGRANULOCYTOSIS IN PATIENTS TREATED WITH THIOURACIL

Author	Series No. of Cases	Agranulocytosis	
		No. of Cases	Per Cent
Astwood[4]	62	1	1.6
Williams and Clute[5]	152	2	1.3
Williams and Clute[6]	247	3	1.2
McGavack et al.[7]	78	2	2.5
Himsworth[8]	22	1	4.5
Tyson et al.[2]	54	6	11.0
Fishberg and Vorzimer[9]	96	1	1.0
Fishberg and Vorzimer[10]	96	4	4.0
Moore[1]	1,091	19	1.74
Bartels and Blizard[11]	405	4	1.0
Lesses and Gargill[12]	62	1	1.6
Morton	80	2	2.5
Total	2,445	46	1.88

* From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

TABLE II

THIOURACIL-INDUCED AGRANULOCYTOSIS—COURSE AND TREATMENT

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
1	24	450	0	Late	?	Pentnucleotide transfusion	Died	7	M. 70. Onset WBC 1250 P37% asymptomatic 2 days—then acutely ill. Penicillin given during terminal 24 hours.[13]
2	7½	300	1	Late	About 225,000	Crude liver, pentnucleotide, bone marrow, transfusions	Died	5	F. 62. Complicating diabetes, thiouracil continued for 3 days after onset. Penicillin started 4th or 5th day after onset[15]
3	13	1,200	0	?	?	Pentnucleotide, transfusions	Recov.	11	F. 61. Angina and ulcerations after 13 wks. of thiouracil disappeared spontaneously in 6 days. Recurrence 3 wks. later. Acutely ill. Recovery followed discontinuance of drug[16]
4	9	850	0	?	?	Liver, transfusions	Recov.	12	F. 63. 2 days after discontinuance of drug developed inflammed nose and throat and fever. Return of leukocytes began on third day without treatment[17]
5	4½	3,500	0	At once	400,000	Transfusions	Recov.	13	F. 50. Headache, sore throat, enlarged glands. Temp. 104°[17]
6	8	2,000	19	?	?	Pentnucleotide—liver extract, sulfadiazine	Recov.	?	M. 40. Sore throat. Temp. 104° chill—acutely ill[18]
7	2½	2,400	4	At once	560,000	Crude liver, transfusions	Recov.	4	F. 52. Thiouracil stopped with WBC 4000, P. 45%, 36 hours later acutely ill—typical agranulocytic angina T. 104. Authors attribute rapid recovery to early intensive penicillin therapy[19]
8	4	1,500	0	At once	1,600,000	Liver, transfusions	Recov.	11	F. 50. The duration of thiouracil medication not clear[9]
9	9	4,250	5	?	?	Pyridoxine intravenously 125–200 mg. daily	Recov.	5	Authors believe pyridoxine has specific action[20]
10	6	360	0	?	?	Continuous sulfamerazine intravenously	Died	3	F. 49. Admitted acutely ill. Penicillin not available[2]
11	8	250	0	Late	680,000	Sulfadiazine	Died	4	F. 59. Acute strep. tonsillitis after 6 weeks of thiouracil. Recovery after sulfadiazine with WBC. 8650, P. 70%. After 17 days of thiouracil developed typical agranulocytic angina with fever[2]
12	8	500	0	At once	About 600,000	Transfusion	Died	4	F. 47. CBC. normal 3 days before admission. 2 days later acute onset with sore throat and fever. Autopsy showed necrotizing pharyngitis and toxic hepatitis[2]

TABLE II (*Continued*)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
13	10	800	0	Late	200,000	?	Died	4	F. 32. 4 days of sore throat, chills, fever and swollen glands before thiouracil stopped. T. 104, died 10 hours after admission[2]
14	5	3,490	1	At once	1,050,000	Liver extract, transfusion	Recov.	7	F. 29. 5 days before admission fever and sore gums and erosions T. 104–105 for 6 days, then abrupt drop. Penicillin intravenously and intramuscularly[2]
15	7	3,250	0	At once	400,000	Transfusions	Recov.	4	F. 50. 2 days before admission slight fever. Following day T. 102 with lesions in the mouth[2]
16	10	1,200	0	At once	1,000,000	Liver extract, transfusions	Recov.	6	F. 43. Sore throat, swollen gums. T. 104 for 5 days, auricular fibrillation and pneumonia. Recovery dramatic on 6th day[2]
17	11½	1,600	7	At once	1,250,000	Transfusions	Recov.	11	M. 58. T. 105 ulcerations of throat. WBC. on admission 1900, P. 1%[2]
18	4	950	6	At once	1,500,000	Transfusions	Recov.	11	M. 53. Leukopenia for 1 day then fever and angina. Desperately ill for 7 days. Peritonsillar abscess drained[2]
19	5	1,100	0	0	0	Sulfathiazole, pentnucleotide, liver extract	Recov.	7	M. 37. Severe pharyngitis—acutely ill. Temp. 105[4]
20	6	?	?	0	0	Transfusions	Died	0	No detail of blood picture[8]
21	5	900	0	0	0	Pentnucleotide, liver extract, transfusion	Died	16	F. 49. Sore throat acutely ill. T. 102 treatment had no appreciable effect on blood picture[21]
22	?	?	?	?	?	?	Recov.	?	Patient seriously ill for several days[5]
23	?	?	?	?	?	?	Recov.	?	Patient seriously ill for several days[5]
24	8	?	?	?	?	?	Died	?	F. Agranulocytic angina. Furuncle on nose 2 weeks before. Thiouracil stopped, and paronychia 1 week prior. Terminal broncho-pneumonia and lung abscess.[3]
25	5	?	?	?	?	?	Died	?	F. Treated privately. Admitted to hospital with agranulocytosis and angina[3]
26	6	?	?	Vigorous systemic treatment			Died	10	Agranulocytosis treated apparently successfully. 4 days after blood count began to rise—patient died of cerebral thrombosis. Thiouracil stopped 10 days before death[3]
27	5	1,000	0	Late	400,000	Fluids	Died	5	F. 41. T. 105. Throat lesions. Died 8 hours after admission to hospital[11]

TABLE II (*Continued*)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
28	11	900	0	At once	1,315,000	Pyridoxine, crude liver	Recov.	10	F. 36. Thiouracil stopped 8 days before symptoms. Penicillin given intravenously, intramuscularly and by spray. 460,000 U. 1st day, 420,000 U. second day, etc. WBC improved 7th day. 10th day WBC 12,000 P. 50%[11]
29	4	1,600	7	At once	Large doses	?	Recov.	14	Penicillin dosage similar to case 28[11]
30	?	?	?	0	0	0	Recov.	?	Mild agranulocytosis. Recovered without treatment[11]
31	4½	900	0	Late	150,000	Sulfanomides intravenously, liver extract, transfusions	Died	6	F. 56. Third course of thiouracil in 1 year. Sore throat. T. 103. Previous courses were 12 weeks and 3 weeks. Thiouracil stopped each time because of myxedema[12]
32	?	?	?	?	?	?	Died	?	Author mentions autopsy in case of agranulocytosis following thiouracil—no details[23]
33	3	400	?	Yes	?	Transfusions	Recov.	?	2 weeks after stopping drug because of leukopenia, patient developed granulocytopenia with T. 106 and cellulitis of finger[10]
34	28	200	0	Late	300,000 intravenously 1st day	Sulfathiazole, crude liver, transfusions	Died	4	M. 34. Sore throat. T. 105 6 days after stopping thiouracil had general malaise-admitted to hospital 2 days later. Died 52 hours after admission[24]
35	7	1,150	2	Late	480,000	Pyridoxine 200 mg. intravenously	Recov.	7	F. 28. Thiouracil discontinued when WBC 3250 P. 21%. 4 days later angina and fever. Author believes pyridoxine an important factor in recovery[25]
36	?	400	?	0	0	Pyridoxine 200 mg. intravenously	Recov.	4	2 hours after pyridoxine WBC rose from 400 to 1800 and in 4 days with daily pyridoxine 200 mg. WBC rose to 4900[26]
37	?	2,000	25	0	0	Pyridoxine 200 mg. intravenously	Recov.	1	M. 28. Author found that 200 mg. pyridoxine doubled the WBC and tripled the polys. in 4 hours[10]
38	?	?	0	0	0	0	Recov.	13	Severe agranulocytic angina-fever-ulcerations of throat-spontaneous recovery with WBC 4500 on 13th day. Control case with case 39[10]
39	?	?	0	0	0	Pyridoxine 200 mg. intravenously	Recov.	2	Similar case to above. Recovery in 48 hours following 6 intravenous injections of 200 mg. each of pyridoxine[10]
40	7	1,000	0	0	0	Sulfadiazine, vit. B, liver extract	Recov.	10	F. 50. Malaise and slight infection of finger. T. 104 for 5 days, few or no granulocytes for 7 days[6]

TABLE II (*Continued*)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
41	6	600	0	?	?	Penicillin, liver extract, pentnucleotide	Recov.	12	F. 31. Sore throat for 3 days. T. 103. Infection subsided in 8 days[6]
42	52	1,000	0	0	0	Liver extract, pentnucleotide. Sulfathiazole ?	Recov.	12	F. 44. For preceding week patient took sulfathiazole for "infections" of skin and mouth, no complaints—no fever—refused hospitalization[6]
43	4	2,100	7	0	0	Pentnucleotide, transfusions	Recov.	27	M. 57. Received thiouracil for heart failure. No lesions. (Borderline case)[12]
44	?	5,000	34	0	0	0	Recov.	?	F. 54. WBC dropped from 10,600 with 6% P. to 4800 with 61% P. and later to 5000 with 34% P. Sore throat. T. 100.5. Recovered on discontinuance of drug. (Borderline case)[12]
45	22	3,000	31	0	0	0	Recov.	?	F. 33. Sore throat, fever and granulocytopenia. (Borderline case)[12]
46	2	4,900	8	?	?	0	Recov.	?	Sore throat. (Borderline case)[26] (3 in discussion)
47	3	600	0	At once	?	?	Rec.	7	Previous thiouracil treatment 6 months ago. Severe pharyngeal manifestations. 7 days complete agranulocytosis[26] (3 in discussion)
48	14	750	0	0	0	Transfusions	Recov.	30	F. 47 with carcinoma of throat was given thiouracil to reduce thyroid nodes. Also had *x*-ray therapy. BMR was normal. Temperature normal[14]
49	6	?	Few	0	0	Pentnucleotide, liver extract	Recov.	?	Patient developed fever and an infected finger. Only a few granulocytes were present for 7 days[27]
50	1	3,900	60	0	0	Pentnucleotide	Died	?	F. 67 with heart failure responded to digitalis and sedatives—was given 0.3 gm. thiouracil by injection daily. Developed leukopenia. Responded to pentnucleotide. Following thyroidectomy died of thyrotoxic crisis[29]
51	?	?	?	Given	?	Crude liver extract, pyridoxine	Recov.	?	Author believes withdrawal of drug and combating concomitant infection with penicillin essential[28]
52	?	?	?	Given	?	Crude liver extract, pyridoxine	Recov.	?	Same as above[28]
53	2	?	?	?	?	?	Recov.	?	Previous thiouracil therapy; possible agranulocytosis during previous treatment at other institutions[3]

TABLE II (*Continued*)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
54	4	3,100	0	?	?	?	Recov.	?	Typical pharyngeal manifestations[3]
55	6	?	0	?	?	?	Recov.	?	Concomitant sulfadiazine therapy for pneumonia[3]
56	6	?	?	?	?	?	Recov.	?	70. Poor response to thiouracil. Also had diabetes mellitus[3]
57	7	?	?	?	?	?	?	?	No details[3]
58	8	?	?	?	?	?	?	?	Concomitant sulfathiazole therapy. No details[3]
59	36	?	?	?	?	?	?	?	No details[3]
60	1	750	0	Late	1,100,000	Pyridoxine, transfusions	Died	14	F. 63. Third course of thiouracil. This report. Details in Table III
61	7	1,000	0	At once	2,250,000	Pyridoxine, liver extract, transfusions	Recov.	11	F. 33. This report. Details in Table IV

(Cases 46, 53, and 61, Table II) (at least two of these three patients had had previous thiouracil therapy) and the longest interval was fifty-two weeks. (Case 42, Table II.)

It is the time element even more than the dosage of thiouracil that determines the possible occurrence of agranulocytosis.[1] The unpredictable nature of this dreaded complication allows no warning of bone marrow depression before the onset of symptoms except by hematologic examination. The importance of close and careful supervision of the white blood count, particularly during the "dangerous" second month, cannot be overemphasized.

The age and sex of the patient are apparently not important factors in agranulocytosis. The youngest patient was twenty-eight years and the oldest seventy years. Of the thirty-seven cases in which there is a record of sex, twenty-nine were women and eight men—a ratio of about 3½ to 1. This closely approximates the incidence in the sexes of the underlying hyperthyroidism for which the thiouracil was administered.

Seventeen of the sixty-one patients died from agranulocytosis. This high mortality rate (28 per cent) emphasizes the need for earlier recognition and more effectual treatment.

In the present series of eighty patients treated with thiouracil for thyrotoxicosis, two developed agranulocytosis.

CASE REPORT (TABLE III)

L. W., a sixty-three-year old white female, had been under medical care for thyrotoxicosis for the past four years. Since January, 1945, she had been treated with thiouracil. On April 7, 1945, the patient developed a slight sore throat and four days later the white blood count was "very low" with a complete absence of granulocytes. At a previous date the patient had had a similar attack of agranulocytosis that had responded to some undetermined treatment. She was first seen by us April 16, 1945, when admitted to the hospital complaining of sore throat, fever and cough.

Examination revealed an acutely ill patient with temperature of 100.6°F.), pulse 140 and irregular, and respirations 36. The throat was inflamed, the tonsils cryptic and covered with exudate. The thyroid was enlarged and firm. Auricular fibrillation with a rate of 160 was noted. No murmurs were heard. The blood pressure was 160/90. Moist coarse râles were

TABLE III

Date	Hb.	RBC.	WBC.	Per Cent Polys.	Medication	Comments
4/16	90	4,350,000	5,200	40	Digitalis gr. ½ t.i.d. oxygen sedation	Patient admitted acutely ill. T. 100.6 P. 140. R. 36 sore throat, cough, thyrotoxicosis—congestive heart failure
4/18	..	.....	3,600	51	500 cc. blood—pentnucleotide 20 cc., Lugol's mx t.i.d. vitamins	BMR. +63%
4/20	..	.....	11,100	75	Stilbestrol 5 mg. twice daily	Attempt to reduce thyrotropic factor by inhibiting anterior pituitary
4/21	..	.....	13,400	85	Aminophyllin. Phenobarbital	
4/23	..	.....	12,800	91	Lugol's solution discontinued	*X*-ray shows cardiac enlargement. No pulmonary congestion
4/24	..	.....	14,200	81		
4/27	95	5,050,000	27,600	84	.....	BMR +49%. Patient better. Heart rate 92 with no deficit. Surgeons suggest thiouracil
5/1	89	.....	18,400	85	Transfusion 250 cc.	
5/2	91	4,850,000	13,500	72	Transfusion 250 cc.	
5/3	90	5,270,000	22,100	89		
5/4	..	.....	25,000	90		
5/15	84	4,490,000	16,400	90		
5/7	83	4,550,000	9,700	83		
5/8	80	4,550,000	8,200	77		
5/9	83	4,300,000	26,000	91	.....	Surgeons found patient to be a very poor surgical risk. Suggested *x*-ray therapy
5/10	80	4,320,000	11,300	75	.....	*X*-ray consultation. *X*-ray therapy inadvisable
5/11	..	.....	16,000	82		
5/12	..	.....	13,000	76		
5/15	75	4,050,000	11,400	69	.....	BMR +76%. Lost 4 lbs. in past 4 days
5/16	78	3,780,000	12,200	81		
5/17	78	4,100,000	10,000	73		
5/18	73	4,310,000	9,900	70		
5/21	78	4,250,000	5,700	67		
5/22	..	.....	5,900	77	.....	BMR +100%. Test not satisfactory. Clinically patient's condition poor
5/23	..	.....	6,900	74	Thiouracil	Thiouracil started 0.4 Gm. every 6 hours, first day. Then 0.1 Gm. 5 times daily. All other medication stopped
5/25	..	.....	8,400	82		
5/28	83	4,300,000	8,700	82		
5/29	75	4,450,000	4,200	57	Thiouracil discontinued. Pyridoxine, intravenous fluids	Medication stopped. *X*-ray shows cardiac enlargement
5/30	75	4,600,000	3,000	28	Pyridoxine 200 mg. intravenously	Sore throat
5/31	78	4,290,000	1,000	11	Fluids. Pyridoxine 200 mg. I.V.	Inflammation more marked
6/1	80	4,300,000	1,350	0	Penicillin 20,000 units every 3 hr. Pyridoxine 200 mg. intravenously	Surgical consultation. BMR +77%
6/2	..	.....	750	0	Pyridoxine. Penicillin	ENT consultation. Severe pharyngitis and tonsillitis with ulcerations
6/3	..	.....	2,100	0	500 cc. blood. Pyridoxine 200 mg. Penicillin I.V.	Surgical consultation. Too ill for surgery
6/4	..	.....	1,800	1	Penicillin. Pyridoxine 200 mg. I.V. Stilbestrol I.V. 10 mg.	Patient's condition still critical
6/5	..	.....	1,450	2	Oxygen. Penicillin. Pyridoxine 200 mg. Blood transfusion.	Severe secondary infection of throat. T. 103°F., P. 140, R. 40
6/6	..	.....	5,000	16	Oxygen. Penicillin. Pyridoxine 200 mg. Blood transfusion	Portable *x*-ray shows fluid in pleural space and bronchovesicular congestion. Patient sinking. Died 10.30 P.M. Total penicillin 1,100,000 units

present in both lung bases. The liver was felt two and one-half fingers below the coastal margin and pretibial edema was present. Rapid digitalization was started and oxygen and sedation were given. The electrocardiogram confirmed the auricular fibrillation with rapid ventricular rate. *X*-ray of the chest revealed enlargement of the cardiac shadow and bronchovesicular congestion. The white cell count on admission was 5,200 with 40 per cent polymorphonuclear cells.

The following day she seemed somewhat improved. She was given 500 cc. of whole blood, vitamins B and C intravenously, pentnucleotide 10 cc. twice daily, morphine sulfate as needed and she was started on Lugol's solution m. 10 three times daily. The basal metabolic rate was +63 per cent. The following day, the white cell count was 3,600 with 51 per cent polymorphonuclear forms of which eighteen were immature. She seemed clinically better, however. Two days later, on her sixth hospital day the white count rose to 11,100 with 75 per cent polymorphonuclears. This was thought to be the "leukocytic hyper-reaction" following agranulocytosis. Lugol's solution was stopped and patient was given 5 mg. stilbestrol twice daily. By April 27th she was clinically much better. The pulmonary congestion was gone. The heart rate was 92 with no deficit. The basal metabolic rate was plus 49 per cent. The laboratory findings were as follows: Blood sugar 153.8 mg. per 100 cc., creatinine 1.2 mg. per 100 cc., creatine 8.58 mg. per 100 cc. or 19.7 mg. in twenty-four hours, cholesterol was 234 mg. per 100 cc. and esters 82.5 mg. per 100 cc. The urine showed a faint trace of albumin. The Wassermann was negative as was the galactose tolerance. The prothrombin time was 26.1 seconds. By April 27th, the fasting blood sugar was 126 mg. per 100 cc. and cholesterol 207 mg. with cholesterol esters 62. The cephalin flocculation test was 1+. The basal metabolic rate was +49 per cent.

The patient's white count remained high and she was increasingly nervous. On May 12th, the basal metabolic rate was +76 per cent and her weight had gone down 4 pounds in as many days. The advisability of *x*-ray therapy arose but on consultation it was believed that the patient's generally poor condition and her tendency to agranulocytosis would make the amount of radiation necessary to control the hyperthyroid state dangerous. In the absence of malignancy and pressure symptoms, *x*-ray therapy was not advised. The patient did not do well and on May 22nd the basal metabolic rate was +100 per cent. Although unquestionably a good part of her high rate was due to the cardiac decompensation, the thyrotoxicosis was severe. At this time the cholesterol was 128.7 mg. per 100 cc. and the cholesterol ester fraction was 82.5. With definite misgivings thiouracil was started on May 23rd (as noted in Table III). At this time the white cell count was 6,900 with 74 per cent polymorphonuclears. On May 28th, the white cells were 8700 with 74 per cent polymorphonuclears. The following day the count dropped to 4,200 with 57 per cent polymorphonuclears. The thiouracil was stopped at once and patient was given 1,000 cc. of 10 per cent glucose immediately and 100 mg. of pyridoxine intravenously twice daily. The following day, May 30th, the white count dropped to 3,000 with 28 per cent polymorphonuclears. The pyridoxine and infusions were continued. A sore throat had developed but no ulcerations were seen. The next day the white count dropped to 1,000 with 11 per cent polymorphonuclears. On June 1st, the leukocytes were 1350 but there was a complete absence of granulocytes. The basal metabolic rate was +77 per cent. She was started on penicillin 20,000 units every three hours and the pyridoxine, 200 mg. intravenously daily, was continued. The surgeons agreed to operate as soon as the agranulocytosis cleared up. The otolaryngologist found a severe pharyngitis and tonsillitis with ulcerations of the throat and advised continued use of penicillin. On June 2nd, the white count rose to 2,100 and the patient was given 500 cc. of whole blood. The following day granulocytes began to appear in the circulating blood. The patient was still acutely ill with a severe secondary infection in the throat. The temperature was 103°F., pulse 140, and respirations 40. The pyridoxine and penicillin were continued. On June 6th, the white count rose to 5,000 with 16 per cent polymorphonuclears but clinically the patient was very low. She was given another transfusion and infusion and continuous oxygen.

TABLE IV

Date	Temp.	Pulse	Resp.	Hb.	RBC	WBC	Polys.	Comment
2/21	.....	74	..	80	4,000,000	6,750	68	Patient has been receiving 4 Gm. thiouracil daily since 1/9/46. White cell count has been normal. BMR +25%
2/28	.....	96	..	78	3,750,000	3,950	0	Patient left before blood count was determined and could not be reached. BMR +14%. Thiouracil 0.3 Gm. daily stopped by telephone
3/1 A.M.	98.6	90	20	77	.....	2,250	0	Patient was given 50,000 U. penicillin and admitted to hospital. On questioning complained of very slight sore throat
3/1 P.M.	98.6	90	20	75	4,400,000	1,050	0	Sore throat, small ulceration of palate and gums. Blood transfusion (500 cc). Saline, penicillin 25,000 U. every 3 hours
3/2 A.M.	100	76	20	99	4,510,000	1,000	0	Folic acid 50 mg. daily. Pyridoxine 25 mg. daily intravenously, crude liver 2 U. every 2 days. Fluids-high vitamin diet. Persistent sore throat. Penicillin 200,000 U. daily
3/2 P.M.	101.4	90	20	80	4,500,000	1,250	2?	Lymphocytes ranged from 89 to 96%. Monocytes 1–4%. Clinical condition same. Not acutely ill
3/3	102.4	110	20	93	4,640,000	1,350	0	Patient complained of soreness of throat and neck. Painful to open mouth. Not toxic
3/4	102	100	20	89	4,880,000	1,300	0	Receiving same medication
3/5	101	90	20	82	4,630,000	1,100	0	Patient comfortable
3/6	100	90	20	84	4,400,000	1,300	0	Folic acid and crude liver extract discontinued. Penicillin 200,000 U. daily as before
3/7 A.M.	100	90	20	85	4,750,000	200	0	Pyridoxine discontinued. 3 Plasma cells, 1 metamyelocyte per 100 cells seen
3/7 P.M.	98.6	84	20	..	.....	2,700	3	3 immature polymorphs noted, 2 metamyelocytes, 3 transitional cells, 84 lymphocytes, 8 monocytes. Penicillin only medication
3/8	97.6	80	18	88	4,770,000	4,000	14	14 polys of which 9 were immature, 4 myelocytes, 1 metamyelocyte, 3 transitionals. Throat very slightly sensitive. Ulcerations healing
3/9	97.6	80	18	89	4,900,000	6,200	21	Mouth and throat much better. No complaints
3/10	98	80	18	85	4,310,000	9,450	34	20 immature cells. 60 lymphocytes. No symptoms—throat clear
3/11	94.4	78	18	90	4,750,000	11,600	46	Penicillin stopped. Patient discharged in good condition
3/16	.....	84	..	90	4,400,000	11,100	54	Patient feels fine
3/29	.....	80	..	83	4,150,000	12,200	65	No complaints

Despite all measures she kept sinking rapidly and expired that night at 10:30 P.M. In all she had received 1,600 mg. of pyridoxine intravenously and 1,100,000 units of penicillin.

CASE REPORT (TABLE IV)

E. K., a thirty-three year old housewife, complained of palpitation, increasing nervousness, fatigue and loss of weight. A subtotal thyroidectomy had been performed twelve years earlier for similar complaints. Several months prior to our seeing her, she had observed an increase in the size of a small mass in the neck. This had been present since 1941 at which time her basal metabolic rate was −4 per cent. Examination in October, 1945, revealed a highly nervous individual with a pulse of 104, blood pressure 100/70 and basal metabolic rate +26 per cent. Her weight was 97½ pounds. She did not respond to sedation and on January 9, 1946, thiouracil therapy was started.

After seven weeks of uneventful treatment, the patient's leukocyte count suddenly dropped to 3,950 cells per cu. mm. with a complete absence of granulocytes. Subjectively there were no complaints. The patient could not be reached until the following morning when the white

blood count had fallen to 2,250 with a complete absence of polymorphonuclear forms. She was given 50,000 units of penicillin and 2 units of crude liver extract. On admission to the hospital immediately thereafter she still felt perfectly well. However, that afternoon she developed a slight sore throat and scattered small ulcerations on the palate. Five hundred cc. of whole blood and 500 cc. of saline were given that day. Twenty-five thousand units of penicillin were administered every three hours. Folic acid, 50 mg. orally, pyridoxine 25 mg. and crude liver extract 2 units intramuscularly were given daily. The first day in the hospital the white blood cells dropped to 1,050 and the following day to 1,000 per cu. mm. By the third day the temperature rose to 102.4°F. and the lesions in the mouth, especially the ulcerations of the lower gum, increased in size and number. The cervical adenopathy was marked. The patient did not appear toxic, however, and complained only of moderate soreness in the mouth and neck. By the seventh day the temperature had dropped to normal, the white cell count had increased to 2,700 and immature granulocytes began to appear. Folic acid and pyridoxine had been discontinued the preceding day. The lesions healed rapidly so that by the eleventh hospital day the patient was discharged as cured. She had received a total of 2,250,000 units of penicillin. The mild reactive leukocytosis (11,600 with 46 per cent polymorphonuclear forms on discharge) persisted for about three weeks.

COMMENTS

With the increasing use of thiouracil in the treatment of hyperthyroidism, it is inevitable that additional cases of agranulocytosis will be encountered. Because this serious complication usually makes its appearance with disconcerting suddenness, its early diagnosis is of extreme importance. During the period from the third to the twelfth week of therapy, when 85 per cent of the cases occur, the possibility of agranulocytosis must be anticipated and carefully guarded against. Unfortunately, even frequent blood counts may not give sufficient warning. Any untoward change in the white cell count, whether it be a gradual diminution in number or a decrease in the granulocytes or even a moderate unexplained leukocytosis (the irritation before the depression of the bone marrow) should call for added caution. The patient should be advised that the slightest evidence of toxicity, such as the mildest sore throat, rise in temperature or malaise warrants notifying his physician immediately and discontinuing the drug until further instruction is given.

With the occurrence of agranulocytosis, the prompt discontinuance of the offending drug and the immediate institution of adequate treatment is essential to recovery. In some instances (Table II, Cases 3, 4, 30, 38, 44, 45) more or less prompt regression of untoward effects followed termination of the medication. Because of the unpredictable course of this disease, such a limited regimen is fraught with danger. In many cases (Table II, Cases 1, 4, 7, 28, 33, 35, 61) the acute onset of symptoms occurred several days following the cessation of medication. To withhold early and intensive treatment because the patient is asymptomatic may result in disaster. (Table II, Case 1.)

Penicillin is by far the most valuable agent used in combating the dangers of agranulocytosis. Patients who succumb to agranulocytosis die, not from the lack of granulocytes *per se*, but from the overwhelming sepsis that results from the slightest secondary infection. The value of penicillin lies in preventing or controlling the secondary infection until the bone marrow recovers and spontaneous regeneration of the granulocytes occurs. This usually takes about six or seven days.

Penicillin must be given immediately upon diagnosis and in adequate dosage. In the report of the Council on Pharmacy and Chemistry[1] 500,000 units per day was rec-

ommended as the most effective treatment for agranulocytosis. This dose exceeds that given any of the patients listed in Table II. Of the ten cases in which penicillin was given early and in doses of 100,000 units or more daily, only one patient died. (Table II Case 12.) It is conjectural whether this death might have been avoided by larger doses.

The value of other supplementary treatment should not be minimized. The use of pyridoxine is gaining increasing popularity with some workers. Cantor and Scott[20] believe that pyridoxine is the liver factor responsible for the granulocytopoietic effect in agranulocytosis. They also believe that pyridoxine is the factor involved in maturation and emigration of polymorphonuclear cells. (Table II, Case 9.) Fishberg and Vorzimer[10] treated three patients with agranulocytosis with pyridoxine intravenously. (Table II, Cases 36, 37, 39.) They found that an intravenous injection of 200 mg. of pyridoxine was accompanied by doubling of the white cell count and tripling of the polymorphonuclear cells within four hours. A patient in a control test (Table II, Case 38) required thirteen days to recover. They concluded that pyridoxine hastens recovery by bringing about a rapid and significant rise in circulating granulocytes. Wilson[25] also believes that pyridoxine played an important part in the cure of his patient. (Table II, Case 35.) However, valuable as this agent may be in shortening the time of absence of the granulocytes from the blood stream, it must be remembered that the significance of this absence lies in the lowered leukocytic defense of the body against infection. Penicillin, we strongly believe, can prevent infection or control its spread during this period of agranulocytosis, whether it be a day or a week.

The value of other agents used, such as folic acid, pentnucleotide, yellow bone marrow and crude liver extract, has not been satisfactorily demonstrated. These agents, if used, should be employed only as adjunct treatment. Most workers use whole blood in the treatment of agranulocytosis. The value of this procedure is unquestioned provided the transfusions are not repeated so frequently as to cause reactions.

The sulfonamides, at times themselves injurious to the bone marrow, should not be used if penicillin is available.

The course of the acute stage of agranulocytosis usually runs about a week. In many cases recovery has been rather dramatic. After days of high temperature and severe toxicity, the patient may awaken on the fifth, sixth or seventh day subjectively and objectively greatly improved, with hematologic evidence of leukocytic regeneration.

Of the seventeen fatalities recorded, ten patients (Table II, Cases 1, 2, 10, 11, 21, 24, 27, 31, 34, 60) either did not receive penicillin or received it late in the disease; in three cases (Table II, Cases 2, 13, 24) thiouracil was continued for several days after the onset of symptoms; in four cases (Table II, Cases 20, 25, 26, 32) little or no details were given.

One patient (Table II, Case 12) has been discussed above. Another patient (Table II, Case 50) recovered from a mild leukopenia but died postoperatively from thyroid crisis. This case is not considered a drug fatality but is included because the author[29] believed that death was due to an uncompensated granulocytopenia. The patient in our series (Table II, Case 60) was critically ill at admission and, although included as a drug fatality, probably would have died from the underlying thyrotoxicosis and heart failure.

SUMMARY

Fifty-nine cases of thiouracil-induced agranulocytosis collected from the literature and two additional cases herewith reported are analyzed and discussed.

The importance of early diagnosis and prompt institution of treatment is stressed.

Penicillin, given early and in massive doses, has been found to be the most effective agent in the treatment of the complications of agranulocytosis.

Adjunct treatment, especially the administration of whole blood and pyridoxine may be of considerable value in hastening the recovery.

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Seminars on Rheumatic Fever

Volume II of The American Journal of Medicine will contain twelve stenographic reports (edited for publication) of seminars on rheumatic fever conducted at the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, New York. The speakers included recognized authorities in the field of rheumatic fever and rheumatic heart disease. The audience who participated in the discussions included general practitioners, pediatricians, cardiologists, public health officers, nurses, and social workers. The symposium was sponsored, in part, by the Nassau County Tuberculosis and Health Association, by the J. and G. Eisenberg Foundation, and by Mr. P. Brenner.

The program follows:

Epidemiology of Rheumatic Fever

Dr. John R. Paul, *Yale University School of Medicine*

Pathology of Rheumatism

Dr. William C. Von Glahn, *Bellevue Hospital and New York University School of Medicine*

Relationship of the Hemolytic Streptococcus to Rheumatic Fever

Dr. Homer Swift, *Hospital of the Rockefeller Institute of Medical Research*

Heredity and Rheumatic Disease

Dr. May Wilson, *New York Hospital and Cornell Medical School*

Clinical Manifestations of Rheumatic Fever

Dr. T. Duckett Jones, *House of Good Samaritan and Harvard Medical School*

Rheumatic Heart Disease in the Adult

Dr. Cary Eggleston, *New York Hospital and Cornell Medical School*

Laboratory and Clinical Criteria of Rheumatic Fever in Children

Dr. Leo M. Taran, *St. Francis Sanatorium for Cardiac Children, Roslyn, L. I., N. Y.*

Diagnostic Value of Roentgenography and Fluoroscopy in the Diagnosis of Rheumatic Heart Disease

Dr. J. B. Schwedel, *Montefiore Hospital, New York*

Electrocardiographic Findings in Rheumatic Heart Disease

Dr. Harold E. B. Pardee, *Cornell Medical School*

Treatment of Acute Rheumatic Fever and Rheumatic Heart Disease in Children

Dr. Leo M. Taran, *St. Francis Sanatorium for Cardiac Children, Roslyn, L.I., N. Y.*

The Rôle of the Medical Social Worker in the Problem of Management and Control of Rheumatic Fever and Rheumatic Heart Disease

Miss Grace White, *The New York School of Social Work, Columbia University*

The Public Health Aspects of Rheumatic Fever

Dr. H. S. Mustard, *Columbia University School of Public Health*

Epidemiology of Rheumatic Fever*

JOHN R. PAUL, M.D.
NEW HAVEN, CONNECTICUT

I AM grateful for the opportunity to come to this institution and to see the excellent and extensive work that has been going on here for a number of years. I am impressed by how much carefully collected information has been accumulated here regarding the important disease which we are to discuss in this seminar. It is also a great personal pleasure for me to be here and to be one of the distinguished group that has been assembled for this series of seminars. I feel humble about it because I am not an authority on rheumatic disease.

One needs only to compare today's knowledge with that of twenty years ago to realize how far we have come in learning about rheumatic fever. When I was a medical student, and that was not long ago, rheumatic fever was regarded as a wholly mysterious disease. We knew something of the Aschoff body, which was considered a unique finding in medicine and one which must be associated with a unique cause. The mysterious character of rheumatic fever as we knew it then, struck terror into the heart of the medical student. Impressions of the nature of rheumatic fever went little further than the old statement by Lasègue, that it was a disease which, "licks the joints and bites the heart."

Since then, in spite of many unsolved problems in this disease, we no longer consider it wholly mysterious. Progress has been made in England and on the European continent, but particularly in the last two decades has work been done in this country. This includes the work of Dr. Homer F. Swift, Dr. Alvin F. Coburn, Dr. T. Duckett Jones, and others, which will, I am sure, be discussed in subsequent sessions of this series of seminars.

Although I plan to limit this discussion to the epidemiology of rheumatic fever, we may include a few words on pathogenesis. We know, of course, that the relationship of rheumatic disease to sore throats has been recognized at least as far back as the early 1880's. It is now well recognized that a sore throat precedes, in most instances, an acute attack of rheumatic fever. But this relationship of sore throats to rheumatic disease is not a simple one, nor is it well described by calling the sore throat a "focal infection." At least, we cannot eradicate rheumatic fever by tonsillectomy, or by removing certain foci. The concept of focal infection as an explanation of the disease was eventually given up.

About the year 1930, the work of Schlesinger in England, and Coburn in this country, indicated that rheumatic fever is often preceded by a particular type of infection, namely, infection caused by the hemolytic streptococcus. This concept has developed over a period of the last fifteen years and we have now reached the stage where we can say, with a fair degree of certainty, that from the epidemiologic standpoint, and perhaps also from the immunologic standpoint, rheumatic fever is in some way related to infection caused by hemolytic streptococci.

The clinical relationship of events preceding a rheumatic attack (Fig. 1) is demonstrable in about one-half of the cases. An acute streptococcal infection, known as phase 1, initiates this sequence. It does not have to be severe and often escapes notice.

* From the Department of Preventive Medicine, Yale University, School of Medicine. Read at St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, October 2, 1945

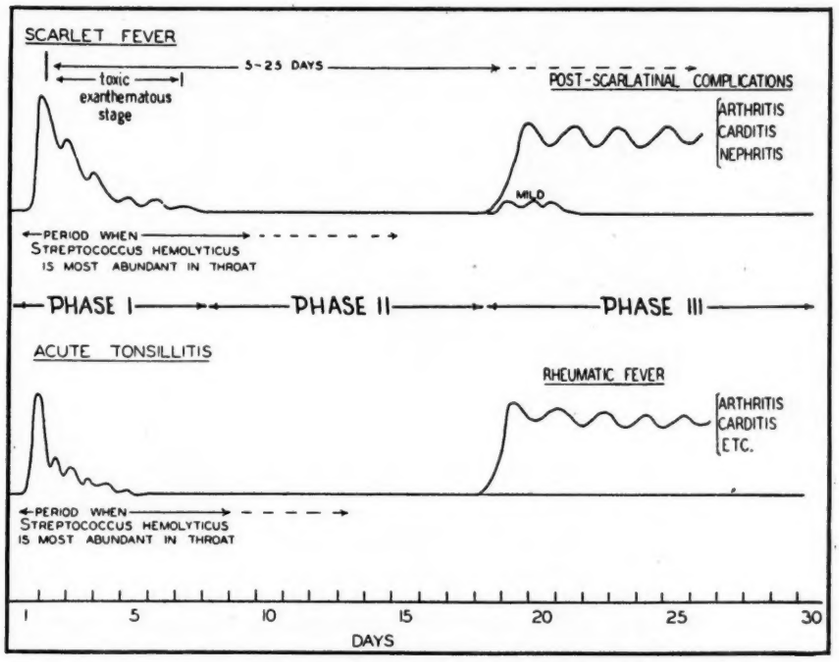

FIG. 1.* Diagrams modified from Escherich and Schick to illustrate the possible forms indicated by temperature curves which the non-suppurative "complications" of scarlet fever and of acute tonsillitis may assume. The division of this process into three phases is also shown.

There may follow a quiescent period, or latent period, lasting anywhere from five to twenty-one days. This is known as phase 2. This in turn is followed by a third phase, which is the period during which rheumatic fever manifests itself. This recalls the events originally observed in the non-suppurative complications of scarlet fever by Escherich and Schick. Here the toxic exanthematous stage is also followed by a quiescent period lasting anywhere from five to twenty-five days, which in turn may be followed by post-scarlatinal complications, such as arthritis, carditis and nephritis. As in scarlet fever, however, it is obvious that only in a small percentage of cases of acute tonsillitis does an acute rheumatic attack subsequently develop.

This "explanation" of the events leading up to rheumatic fever is not final. It neglects the possibility that reinfection by multiple strains of streptococci may also play some part. But that is theoretical and not final either.

A classic example of rheumatic disease following hemolytic streptococcal infection is presented by a milk-born epidemic in Denmark in the year 1926. (Fig. 2.) It appears from this chart, that this epidemic began at the end of November and rose to the peak in a few days. About three weeks after the peak of this epidemic of hemolytic streptococcal infection, cases of rheumatic disease made their appearance and the incidence of such cases increased for the next two or three weeks. This type of sequence has been seen both here and in other countries over and over again. Such experiences were common in military installations in this country during the war.

The repeated occurrence of streptococcal sore throat epidemics followed by increasing incidence of rheumatic disease is strong evidence of a relationship between the two. Most of the epidemics of rheumatic fever that have been reported, have apparently

* Permission has been granted by the Metropolitan Insurance Co. to reproduce Figures 1 to 9.

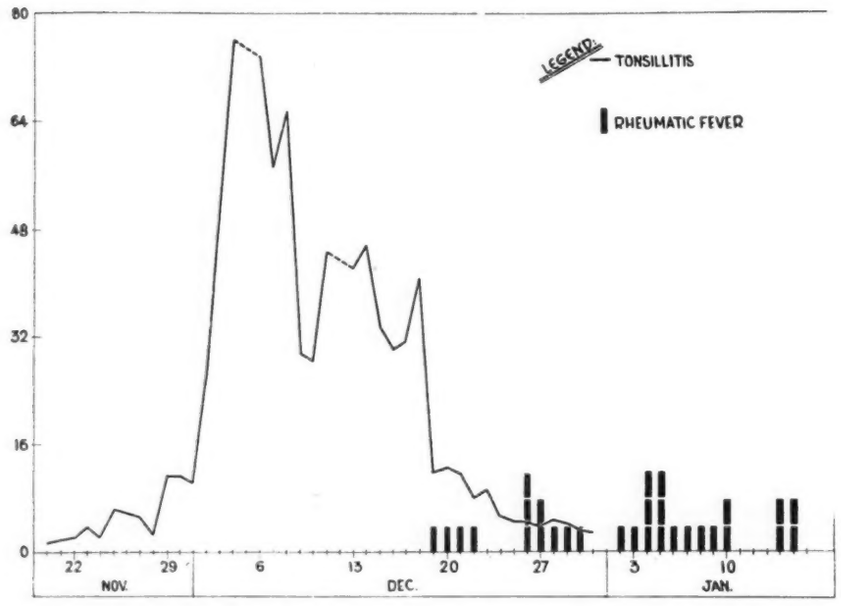

FIG. 2. Severe milk-borne epidemic of hemolytic streptococcal infection which occurred in Denmark in 1926. The scale on the left indicates the daily number of cases of tonsillitis. Late in the epidemic, thirty cases of rheumatic fever appeared. (From Madsen and Kalbak. *Acta. path. et microbeal. Scandinav.*, 17: 305, 1940.)

followed epidemics of streptococcal infections, and from all this it becomes apparent that a "good" year for hemolytic streptococcal infections is a "good" year for rheumatic fever.

Much can be learned about this disease from observing families, as was done in the study represented in Figure 3. Here we see that five members of the same family have suffered an acute attack of streptococcal infection. Their illnesses began about the same time: one member with an acute sore throat followed by otitis media; another with a scarlatina form rash at the time of the acute infection; a third member with a long attack of tonsillitis which subsided without sequellae in a week or ten days, and a fourth member with tonsillitis of short duration; a fifth member had a sore throat which was followed by a latent period of several days and subsequently, by a rheumatic attack.

Thus, it is apparent that this same type of initial infection may manifest itself in different ways in different members of the same family. In some families there is stronger predisposition to rheumatic fever than others, the susceptibility for rheumatic attacks following streptococcal illness being apparently greater than in other families.

The multiple courses that the disease may take from its onset will not be discussed here. No doubt, this will be covered by various other members of the seminar. But let us turn now to the size of the problem in this country. Where does it flourish best and what are the geographic and sociologic factors which encourage its spread? What are the circumstances under which it is most prevalent?

Type A streptococcal infection may be food-borne or milk-borne, but there is no special vector or medium such as the mosquito, or the louse, necessary for the transfer of the infection from one person to another. In other words, it is a crowd disease, and a contact disease, similar to many of the respiratory infections. Crowded dwellings or the herding together of susceptible children or adults leads to the spread of

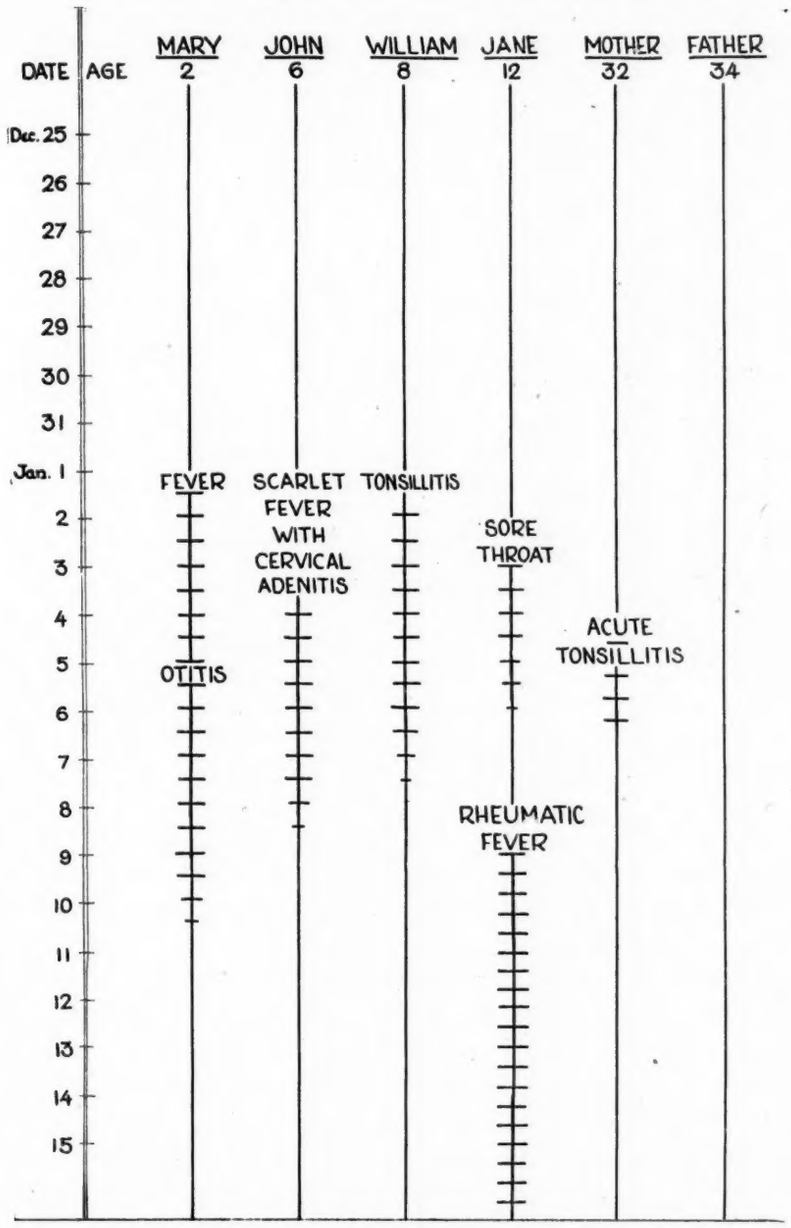

FIG. 3. A family composed of two parents and four children in which an epidemic of acute hemolytic streptococcal infection occurred. In each individual the disease expressed itself in a different form. One finds that in infancy and young childhood hemolytic streptococcal infections are often a long disease (three to six weeks) accompanied by suppurative complications. This may be in some contrast to the shorter (and more acutely prostrating) disease which is more characteristic of late adolescence and young adult life. In one child (Jane) the streptoccal illness was followed by rheumatic fever.

such infection; as for instance, the sharp increase of upper respiratory infections when school opens.

It is not easy to determine the prevalence of rheumatic disease. It is not a reportable disease in most parts of this country. Attempts have been made to make it reportable in some United States cities,

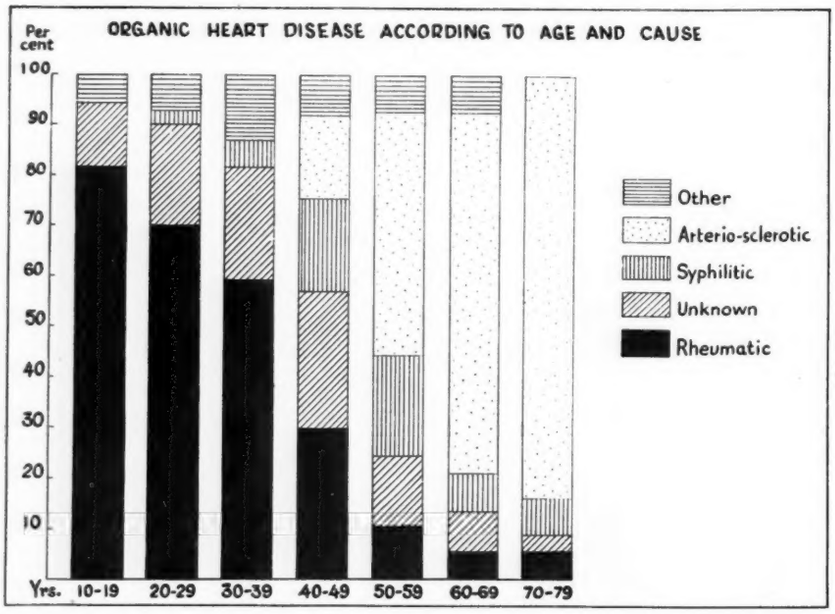

FIG. 4. Relative frequency of different types of organic heart disease at different ages. The sample consists of 1,001 cases, of which 85.4 per cent were clinic patients (Cardiac Clinic for Adults, Bellevue Hospital, New York City) and 14.6 per cent private patients from the practice of the late Dr. John Wyckoff, of New York City. (From Wyckoff and Lingg. *Am. Heart J.*, 1:446, 1926.)

but so far without much success. The reason for this failure is apparent. Even the physician himself is not yet convinced why he should report rheumatic fever since it is not really evident to him that by so doing he may protect the community. Furthermore, it is difficult to be certain of the diagnosis and the physician often does not want to commit himself by reporting questionable cases to the Health authorities. He cannot rely on established laboratory tests such as exist in syphilis or tuberculosis, for instance. Perhaps we should rather make *rheumatic heart disease* reportable instead of *rheumatic fever*. Here we are on somewhat surer ground with regard to diagnosis. Much education and thought on this subject is still necessary.

We can learn more from mortality than from morbidity statistics. These, too, however, are variable. Nevertheless, *most children who die of heart disease, die of rheumatic heart disease.* Some, of course, die of congenital heart disease but it is established that fully 80 per cent of deaths from heart disease in children under fifteen years of age are due to rheumatic heart disease. (Fig. 4.) If then, we study the prevalence of juvenile cardiac mortality, we obtain a fair estimate of the prevalence of rheumatic fever in general. In this way, we have gotten some notion as to how extensive this disease is.

From hospital admission figures, we can also learn something about the prevalence of rheumatic fever by determining what proportion of admissions to the medical or children's wards have rheumatic disease. This proves to be from 1 to 5 per cent of the patients on the general medical service. As far as hospital admissions are concerned, a ten-year study at the New Haven Hospital (1929–1938) showed that cases of rheumatic fever, both active and inactive, constituted the third largest number of admissions for "infectious diseases." (Fig. 5.) Tuberculosis heads the list, syphilis stands second, and rheumatic fever third. Even if only the active cases are included, one is

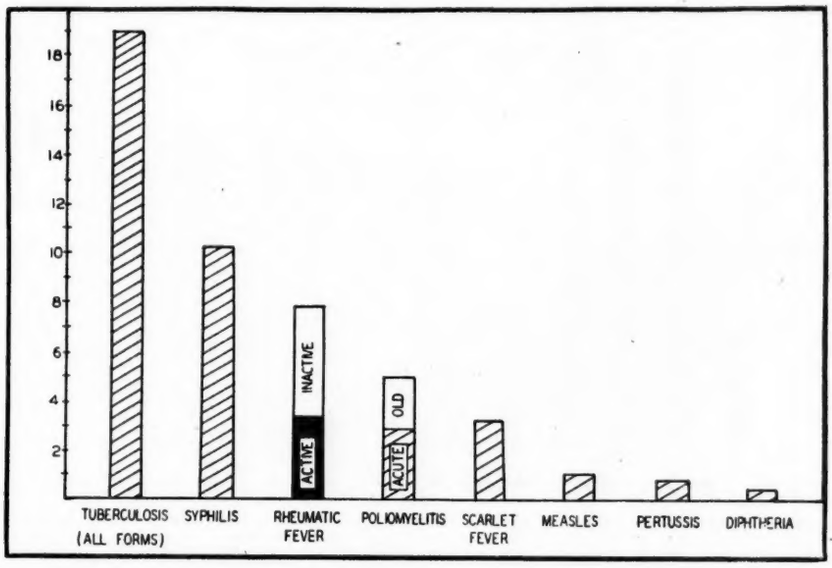

FIG. 5. Comparative rates at which cases representing eight different chronic and acute infectious diseases were admitted to the New Haven Hospital during the period 1929–1938. (From Paul. *Am. J. Pub. Health*, 31:611, 1941.)

still confronted with the fact that this disease contributes a very large proportion of the patients admitted to certain general hospitals. Thus, rheumatic fever stands high in the list of disabling diseases.

Finally, something may be learned of this disease from sample studies on the physical examinations of school children. Such examinations may be indicative of how prevalent juvenile rheumatic heart disease is. Some believe that the diagnosis of rheumatic fever cannot be made by a cursory or a single examination of a child's heart at school. There is much to be said on this side. On the other hand, careful studies of this type seem to show that important data on the prevalence of rheumatic heart disease in childhood can be obtained. In the temperate zone, figures run from 1 to 4 per cent.

Age is a predisposing factor in rheumatic disease. Some years back, Wyckoff in New York City analyzed 1,000 cases of heart disease and classified them according to age. (Fig. 4.) In the childhood age group, that is, between ten and nineteen years of age, he found that eight of every ten cardiacs had rheumatic heart disease. He also found that, as age increased the relative prevalence of rheumatic heart disease decreased and, at the same time, the relative prevalence of heart disease from other causes increased. This aspect of the disease emphasizes that rheumatic heart disease is a childhood disease or at least begins in childhood. Clinical experience has also corroborated the fact that the greatest incidence of acute rheumatic fever is found among children rather than adults. (Fig. 6.) Many studies have shown that the ages of greatest susceptibility for the onset of this disease are the school age years. First attacks usually occur at about the age of six. High susceptibility is maintained up to puberty and then it rapidly declines. Once the child has had a rheumatic attack, the chances for recurrence are much greater than is the case in one who has not as yet had a first attack. It has further been shown that certain manifestations of rheumatic disease are most prevalent at certain ages. Chorea, for instance, is one of those examples; it is rare to find chorea after twenty-five years of age. (Fig. 7.)

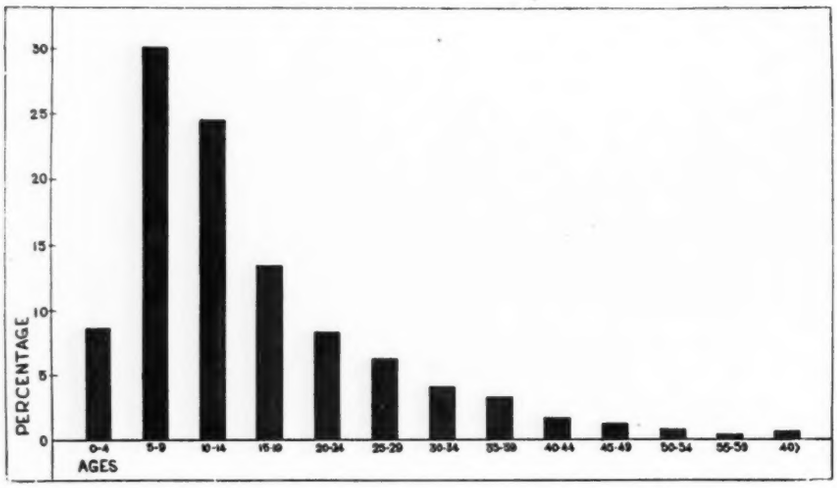

FIG. 6. Percentage distribution by five-year periods of 2,539 first attacks of rheumatic fever with or without rheumatic heart disease, based on past or present histories, among cases admitted to Philadelphia hospitals from January 1, 1930, to December 31, 1934. (From Hedley. *Pub. Health Rep.*, 55: 1647, 1940.)

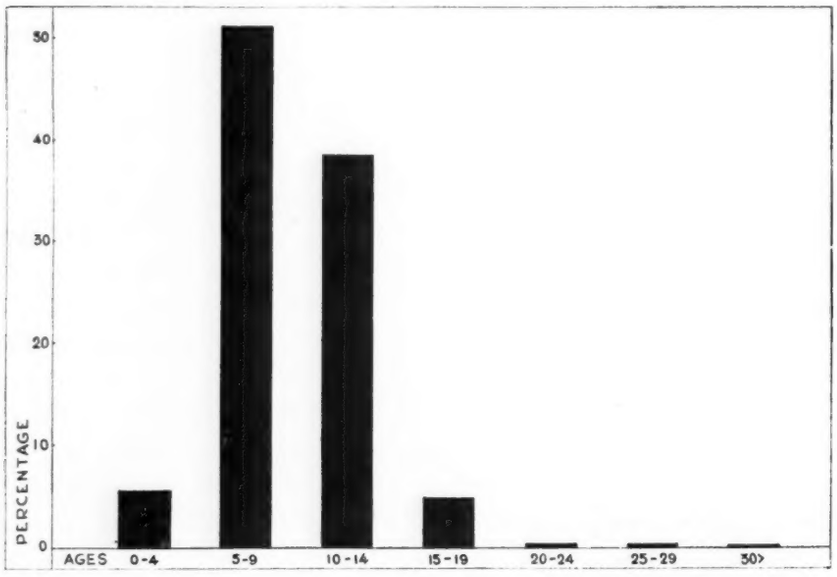

FIG. 7. Percentage distribution by five-year age periods of 920 first attacks of Sydenham's chorea, with or without rheumatic heart disease, based on present or past history, among admissions to Philadelphia hospitals from January 1, 1930, to December 13, 1934. (From Hedley. *Pub. Health Rep.*, 55: 1647, 1940.)

Some idea as to the geographic distribution of rheumatic disease may be obtained from mortality statistics. Studies were made by the Metropolitan Life Insurance Company for the years 1937–1939. (Fig. 8.) In order to avoid the inclusion of other heart disease as much as possible, the Metropolitan Life Insurance Company chose the age group of five to twenty-four. It becomes obvious from this study that certain areas, for instance, Colorado and Utah, New York, Pennsylvania and Massachusetts, have a much higher mortality rate from rheumatic heart disease than do other areas. It was also evident from this study that the southern states, particularly the Gulf States, have a very low incidence of rheumatic heart disease. This geographical distribution

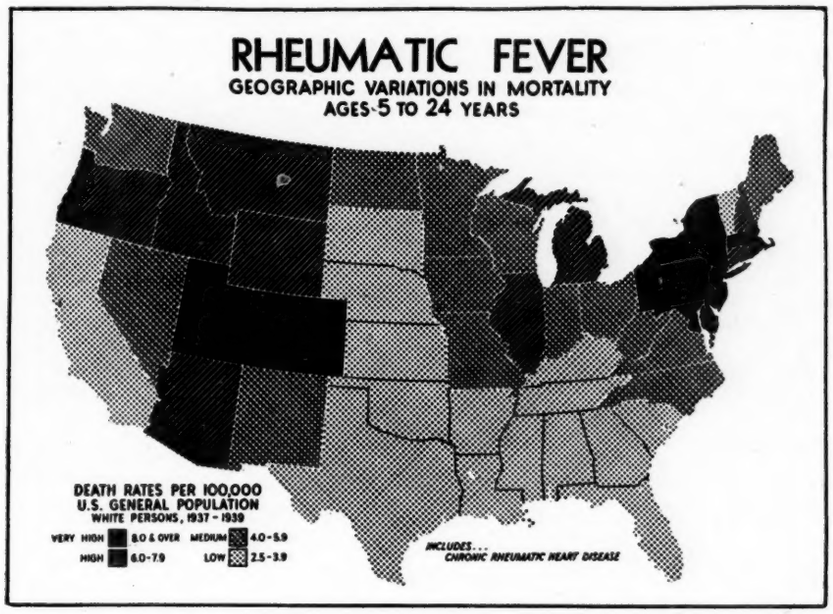

FIG. 8. Map of the United States showing rheumatic fever mortality statistics in the five to twenty-four age group in white persons, for the years 1937–1939, compiled by the Metropolitan Life Insurance Company.

was borne out, in certain instances, by the experience in the Air Forces in the recent war.

Much has been said about the relationship of rheumatic disease to climate. It is incorrect to say that the disease does not occur in warm dry climates but one can say that it certainly is not as prevalent there. We have had occasion to make personal observations on this question in Southern Arizona and in Egypt. New cases appear in such regions but they are not as prevalent as in London or New York City.

In the study of the epidemiology of any disease, racial factors should be discussed. Not much is known about this in rheumatic fever. In New York City and vicinity, two studies indicate that the Irish race seems to lead in the tendency to acquire this disease. Negroes acquire it a little less often than do white people but when they do have the disease, it is apt to be more severe.

Reference has already been made to the fact that much has been learned about the familial character of this disease. One cannot escape the fact that rheumatic fever runs in families. The hereditary factor appears to be somewhat like that in tuberculosis. On the other hand, we are quite aware that besides hereditary traits, other things "run" in some families, such as *Pediculus capitis* for instance. One can say therefore that those circumstances which concern both the host and his environment, and which favor the spread of contact infection in families, must be considered in evaluating familial prevalence in this disease. Studies by Wilson et al. seem to lead one to believe that rheumatic disease is transmitted along with other hereditary characteristics. I am inclined to subscribe to the concept that the tendency to acquire rheumatic fever is the thing that is inherited rather than the disease process itself.

The environment in which a patient lives is often a factor contributing to the spread of the disease. In Germany, as far back as 1880, rheumatic disease was thought to be a disease of certain districts. Elsewhere it was stated that slum living conditions invite a high incidence of rheumatic disease.

Dr. Hedley has also observed that the

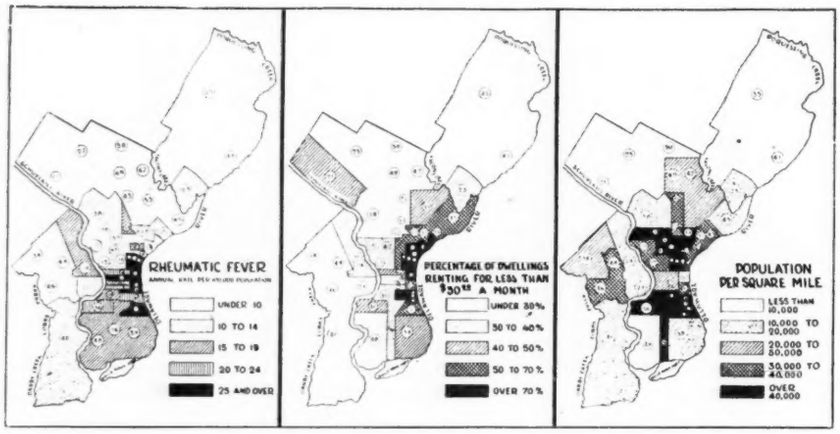

FIG. 9. Maps of the city of Philadelphia, showing, on the left, the distribution by wards of cases of rheumatic fever admitted to Philadelphia hospitals (1930–1934) based on the mean annual number of cases per 100,000 population; in the middle are the low-rental dwellings, and on the right the index of crowding. (From Hedley. *Pub. Health Rep.*, 55: 1845, 1940.)

rate was high in bad urban living conditions in Philadelphia. Some of the criteria for bad living conditions were: crowding, poverty, low rentals, etc. (See Fig. 9.) The same thing was found by workers in Cincinnati, where crowded districts, which were occupied by Negroes at the water front, had a high incidence of rheumatic disease. As in the study of a number of diseases, one can find that crowding predisposes to their spread. Tuberculosis, for instance, is very commonly found in slum districts. While it cannot be said that poverty, per se, is a contributing factor in promoting the spread of rheumatic fever, it can fairly be said that circumstances associated with poverty seem to contribute to the spread of this disease as well as others. Many children in poor homes sleep in the same bed; this is conducive to the spread of disease. Dampness has also been labeled as one of the factors contributing to the spread of rheumatic disease. Poor families are more likely to live in damp houses than are rich families.

In *conclusion*, one can say that the circumstances under which rheumatic fever occurs are similar to the circumstances under which streptococcal infection occurs. This similarity is due to a common cause.

Methods of determining the prevalence of rheumatic fever have been mentioned and some of the situations in which this disease seems to be most prevalent have been pointed out. It is important to know about these situations and to analyze them because such knowledge may have some bearing on the control of this disease.

DISCUSSION

DR. TARAN: The subject of the epidemiology of rheumatic fever is now open for discussion. Are there any questions?

QUESTION: If it is true that rheumatic disease flourishes under certain circumstances which are conducive to other diseases, can one infer that when streptococcal infections occur in conjunction with rheumatic disease that both diseases are the result of a common circumstance and are not related to each other as cause and effect?

DR. PAUL: One cannot infer a common cause because the two diseases exist together but I think the causal relationship between the two diseases is clear from other reasons. It is safe to say that there has never been an epidemic of rheumatic fever without a preceding episode of streptococcal infections. It is true, though, that many strepto-

coccal infections are not followed by, or associated with, rheumatic fever.

QUESTION: What is your opinion about the allergic concept of rheumatic fever?

DR. PAUL: It is an interesting and important theory. It is the theory that both Dr. Swift and the late Dr. Zinsser developed some years back. I believe that the factor of sensitivity to streptococcal products plays an important part in the pathogenesis of this disease. It is a long and complicated subject. Perhaps Dr. Taran can tell us more about the allergic concept.

DR. TARAN: Many years back, the pathologist suspected that the tissue reaction found in rheumatic disease is similar to the tissue reaction found in allergic states. And more recently, the work of Rich and Gregory in Baltimore, seems to show that the tissue reaction in animals in whom anaphylactic shock was produced, was very similar to Aschoff bodies. There is no agreement on this finding.

From the immunologic standpoint, much remains to be learned about the antigen-antibody reaction often found in the blood serum of a patient with acute rheumatic fever. This immunologic response frequently simulates that following a streptococcal infection. That this immunologic response may be responsible for the evolution of a rheumatic attack is not clearly borne out in our experience.

DR. PAUL: For the present, we might say that we have at least two new ways of measuring immunologic reactions in the blood of the rheumatic patient—the antistreptolysin and the antifibrinolysin titers. Both are also characteristic of type A streptococcal infections. These relatively non-specific antibodies, however, are difficult to measure and the technical difficulties might account for some of the discrepancies found by various investigators. There are probably other antibodies as yet undiscovered. Students in the field believe that few discoveries would be more important than to find a method for analyzing immunologic reactions in these patients.

QUESTION: Is it not true that the Streptococcus hemolyticus is a common organism and is distributed widely among the human race and yet not every one that is infected with the Streptococcus hemolyticus comes down with an attack of rheumatic fever?

DR. PAUL: Every one in this part of the world comes in contact with type A streptococci sooner or later. Rheumatic patients, we will say, react in a peculiar manner to the hemolytic streptococcus. I think it is safe to estimate that at least 3 per cent of the young people in our part of the world, when infected with Streptococcus hemolyticus, react with a rheumatic response.

QUESTION: What are the criteria for hemolytic streptococcal infections? What do we mean by an epidemic of hemolytic streptococcal infection?

DR. PAUL: The commonest streptococcal infection is probably acute tonsillitis. An epidemic of tonsillitis is sometimes called streptococcal (or septic) sore throat. There are many other forms, including scarlet fever.

In brief, an epidemic of streptococcal infection consists of a group of illnesses caused by type A hemolytic streptococci, and concentrated as to location and time of occurrence.

QUESTION: How often does one find in civilian life a positive streptococcal throat culture?

DR. PAUL: That depends on many circumstances. I believe that it is safe to say that in New York City in the winter time, one out of every four children or young adults might have, at some time or other, a positive throat culture for streptococcus hemolyticus. It is important to state at this point, that in recent years, the nose culture has been found to be of greater epidemiological importance than the throat culture. The nasal carrier of type A streptococci is apparently more dangerous than is the throat carrier.

The Pathology of Rheumatism

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RHEUMATIC polyarthritis was known to Hippocrates for he has given a description of arthritis that moved rapidly from joint to joint. The name rheumatism, however, was applied to the disease first by Ballonius[1] in a treatise that was published in 1635, twenty years after his death. Sydenham (1676)[2] gave an exact clinical description and stated that "at times it afflicts this or that joint; at other times the inward parts." He also described the chorea. Boerhaave (1737)[3] mentions that "rheumatism invades sometimes the brain, lungs and bowels." Störck (1762)[4] recognized the pleurisy of rheumatism. Stoll (1788)[5] also spoke of rheumatic pleurisy and rheumatic peripneumonia. Pitcairn (1788)[6] described the pericarditis due to rheumatism. Jenner[7] was well aware of the damage done to the heart by rheumatism.

Our modern literature on rheumatism may be said to begin with the writings of Bouillaud (1837–40).[8] Meynet (1875)[9] described the occurrence of subcutaneous nodules and shortly thereafter a more complete description of these was given by Barlow and Warner (1881).[10] The involvement of the myocardium was described by Besnier 1876, Hardy 1876, West 1878 and Goodhart 1879.[11] Romberg (1894)[12] appears to have been the first to recognize inflammatory lesions in the myocardium. Poynton (1899)[13] described what we now call the submiliary nodule but seemingly did not appreciate its specificity. It was Aschoff (1904)[14] who pointed out the specificity of this submiliary nodule now generally called by his name.

ASCHOFF OR SUBMILIARY NODULE

The most specific lesion of rheumatic disease is the Aschoff nodule. In the formation of the nodule the initial damage appears to be to collagen that swells and fragments. About these fragments there collect small nononuclear wandering cells, and with them, in some instances a few polymorphonuclear leukocytes. Later appear the more characteristic large cells, the so-called Aschoff cells; these have a faintly basophilic cytoplasm and a large vesicular nucleus with a prominent chromatin mass in the center. Many of these cells have but a single nucleus, others have multiple nuclei. As these larger cells accumulate, the smaller cellular components disappear; finally in the well developed nodules only the larger cells are found. (Fig. 1.)

In preparations of myocardium suitably stained to show the reticulum fibers, the latter are found to be spread apart by the accumulated cells but are not ruptured. As the nodule becomes older, the characteristic cells assume a more spindle shape; they come to resemble more closely connective cells. Collagen is laid down and finally a dense avascular scar remains to indicate the site of the nodule.

There is some dispute as to the nature of the so-called Aschoff cell. Aschoff considered them to be derived from the large mononuclear cells. Letulle, Bezançon and Weil[15] thought they came from heart muscle, but such an origin could not be invoked for those nodules found in other situations than myocardium. In a recent study Clawson[16] concluded they were modified histiocytes.

* From the Department of Pathology, New York University College of Medicine.

Their function is also obscure. Almost always they are in apposition to the fragments of collagen, and their contour on the side adjacent to the collagen conforms to that of the fragment of collagen. Perhaps they may be in the nature of foreign body giant cells, though in only one instance have I seen a fragment of collagen engulfed by an Aschoff cell.

How long an Aschoff nodule may remain unhealed is a matter for conjecture and the question must remain unanswered until the lesion is undeniably reproduced experimentally. Coombs[17] believed them to be of short duration. The submiliary nodule has many points of similarity with the subcutaneous nodule and these persist for a few weeks; so it is probable that the submiliary nodule heals in approximately the same length of time. It is not unusual to find nodules in the myocardium when there has been a long interval since the last attack of arthritis. I have seen typical nodules in the myocardium when the last attack of arthritis was forty-four years before the death of the individual. It would seem more reasonable to assume that the myocardium was being repeatedly damaged than to infer that the nodules had persisted since the last attack of polyarthritis.

Aschoff nodules are widely distributed. In the heart they are found close to the branches of the coronary arteries, especially in the posterior portion of the left ventricle and in the interventricular septum. In these situations they may be very numerous, or it may be necessary to search carefully to find a few of them. They occur in the endocardium, the substance of the valves and the parietal and visceral pericardium. Nodules have been described in the adventitia of the aorta and pulmonary artery (Pappenheimer and Von Glahn,[31] Paul[27], Meltzer[32]) and in the galea aponeuratica (Tilp,[18] Jacki[19]). Klotz[20] mentions that he has seen them in the subcutaneous tissue, diaphragm, pulmonary artery and aorta. I have seen them in peri-esophageal tissue and near an intercostal artery and also in the diaphragm. (For more complete discussion concerning the Aschoff nodule the reader is referred to the review of Clawson.[21])

Rarely, widespread necrosis of the myocardium occurs with the Aschoff cells scattered throughout the necrotic area. Such a lesion was found in the heart of a child three years of age, together with dense avascular scars of corresponding size.

RHEUMATIC ENDOCARDITIS

The characteristic recent vegetation is a small wart-like mass having a dull yellow color and roughened surface. These verrucae often extend as a chain along the line of closure of the tricuspid, mitral and aortic leaflets; they are less frequently found on the pulmonic cusps. Sometimes flatter, broader, less wart-like vegetations are seen on the mitral valve. The vegetation in the early stage is composed of a granular material that is believed by many to be fibrin. I have not been able to demonstrate fibrin except at the surface where the vegetation is in contact with blood and at the base where it joins the underlying tissue. As the vegetation becomes older the material of which it is composed is more compact. In the earliest stage the vegetation is tough and does not break away readily, hence infarcts in distant organs are not seen in uncomplicated rheumatic cardiac disease. (Fig. 2.)

Healing of the vegetation takes place by the ingrowth of connective tissue from the valve. It is not unusual to find dense bits of the vegetation buried in the connective tissue with more recent and less dense granular material on the surface. Endothelium grows over the surface as healing progresses. Finally the vegetation is completely replaced by connective tissue and covered by endothelium; it is then grey, smooth and translucent.

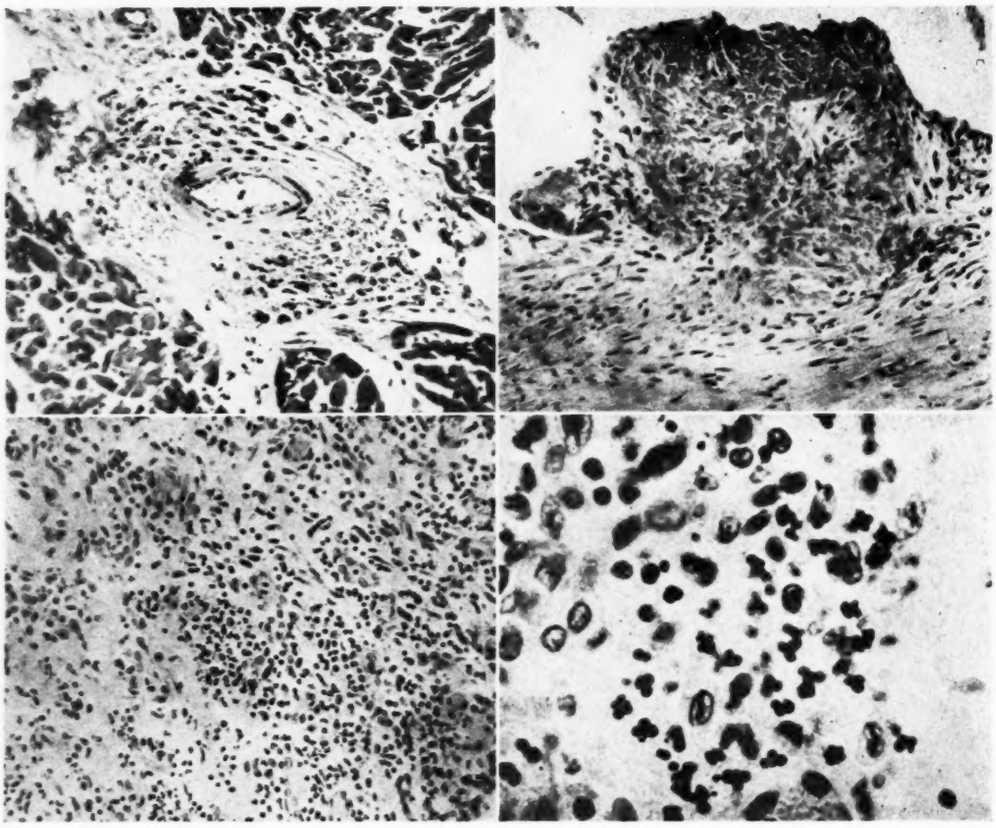

FIG. 1. Acute rheumatic myocarditis; Aschoff bodies.
FIG. 2. Rheumatic verruca; mitral valve.
FIG. 3. Acute rheumatic interstitial valvulitis; mitral valve (low power).
FIG. 4. Acute rheumatic interstitial valvulitis; mitral valve. High power magnification of central portion of Figure 3.

Other and more important changes occur within the valve leaflet; these have been emphasized by Coombs,[53] Swift,[22] and Kugel and Epstein.[38] Aschoff nodules are infrequently found within the valve. More often there is a diffuse inflammation characterized by polymorphonuclear leukocytes, eosinophils and large and small mononuclear cells. (Figs. 3 and 4.) When the endothelium is damaged the vegetation forms. Following the acute interstitial valvulitis there is an increase of connective tissue within the leaflet and blood vessels penetrate into the base of the valve.

Undoubtedly this acute interstitial valvulitis is repeated and increase of connective tissue follows each attack. It is not the healing of the vegetation but this scarring of the valve that is responsible for the thickening, fusion and retraction of the leaflets. Calcium is often deposited in the damaged leaflets and renders them still more inflexible. Similar inflammation and subsequent scarring take place in the chordae tendineae and cause them to shorten, thicken and fuse together. In some instances the chordae are so shortened that the tip of the papillary muscle is brought close to the edge of the leaflet.

In the auricular endocardium a now well recognized form of endocarditis may be found. The surface of the left auricular endocardium is thrown up into irregular ridges and folds, most often above the posterior leaflet of the mitral valve; similar irregularities may be continued across the

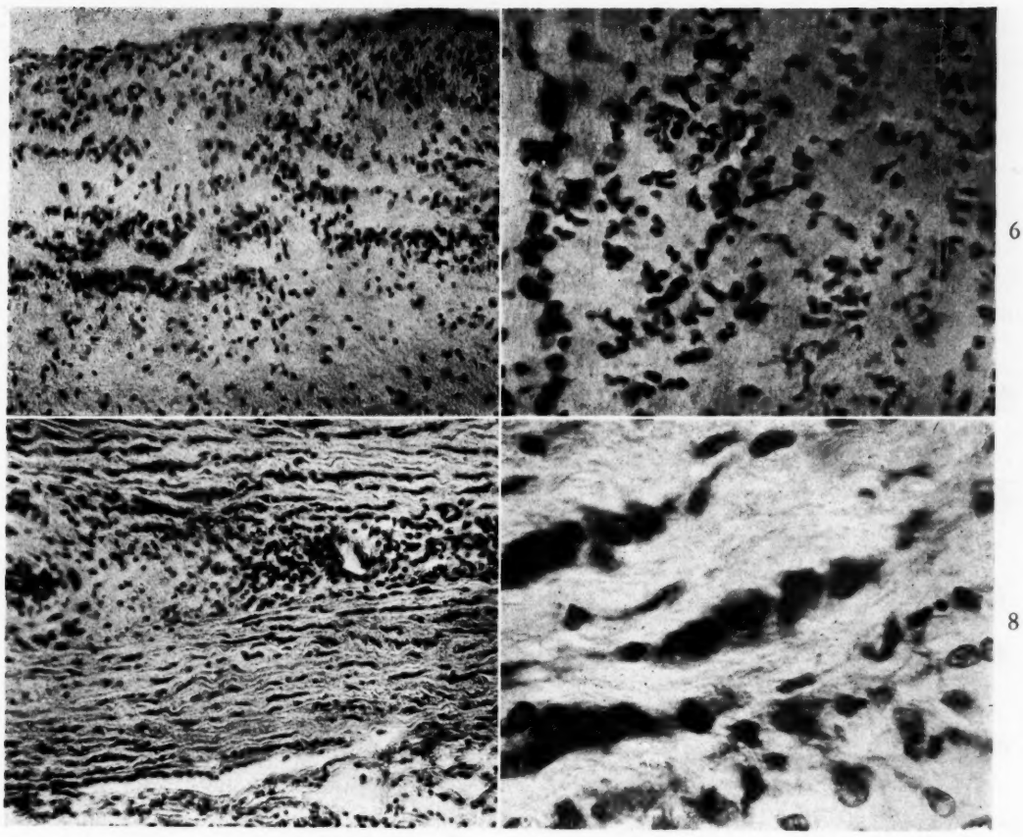

FIG. 5. Rheumatic endocarditis; left auricle; palisade of large cells about altered collagen.
FIG. 6. Rheumatic endocarditis; left auricle; acute reaction; many cells having distorted nuclei.
FIG. 7. Rheumatic aortitis; large cells held in rows by elastic fibers of media; acute reaction about penetrating vessel.
FIG. 8. Rheumatic aortitis. High power magnification of field in Figure 7; large cells held in rows by elastic fibers.

auricular surface of the leaflet to the line of closure. In other parts of the auricular endocardium rounded or oval elevated placques may be found. In the acute stage, the involved endocardium is tawny yellow and dull, in the later stage grey and glistening. Calcium is at times deposited in these lesions.

As elsewhere, the initial stage is swelling of the collagen. Large cells collect about the bands of altered collagen in a palisade fashion. (Fig. 5.) Occasionally an Aschoff nodule is found but usually the elastic fibers hold the cells in rows. With these large cells are neutrophilic and eosinophilic leukocytes and small mononuclear cells.

Also other and equally characteristic cell accumulations are described. These consist of polymorphonuclear leukocytes, small mononuclear cells and large cells differing from the typical Aschoff cell. These large cells are pale staining and the vesicular nucleus has a delicate membrane; the cytoplasm is not basophilic and the nucleolus is small. Always the long axis of the cell is perpendicular to the endocardial surface. Many distorted, elongate and bizarre nuclei are found in these accumulations; they are in part the nuclei of deformed polymorphonuclear leukocytes, others belong to the large mononuclear cells. (Fig. 6.) The cell collections frequently lie in the inner part of the endocardium. When the endothelium is damaged a vegetation forms.

The elastic fibers are spread apart, stretched, fragmented or ruptured by the cell accumulations. In healing an avascular connective tissue springs up that is directed perpendicularly to the surface and penetrates into any vegetation present. Delicate elastic fibrils are later found in this connective tissue and follow its direction. Calcium may be deposited in the later stages.

The outer portium of the endocardium is edematous; fibrin and polymorphonuclear neutrophiles and eosinophiles are found here. Healing takes place by an ingrowth of granulation tissue from the adjacent myocardium that penetrates for a short distance into the endocardium (Claude and Levaditi,[23] Harper,[24] Hertel,[25] Stewart and Branch,[26] MacCallum,[27] Von Glahn[28]).

In a series of eighty-seven hearts Gross[29] found histologic evidence of auricular endocardial damage in each heart.

PERICARDITIS

The characteristic fibrinous exudate may cover the entire surface of the heart or be restricted to a small area at the base. The parietal pericardium is correspondingly involved. With the fibrin there may be a very small quantity or a large amount of fluid. Granulation tissue grows into the exudate from the myocardium and parietal pericardium and may lead to obliteration of the pericardial space with permanent union between the heart and parietal pericardium.

RHEUMATIC DISEASE OF BLOOD VESSELS

Numerous observers[30–36] have given description of the damage done to the aorta in rheumatism. Nodular Aschoff bodies are found in the adventitia or scattered Aschoff cells are observed at the junction of adventitia and media. Large cells held in rows by the elastic fibers are found in the media and along the course of the vasa vasorum. With these large cells are frequently seen polymorphonuclear leukocytes. (Figs. 7 and 8.) The elastic fibers are fragmented in the immediate neighborhood, but the fragmentation is not so extensive as that seen in syphilitic aortitis. Dense avascular scars surround the nutrient vessels when the lesion heals.

Pappenheimer and Von Glahn,[31] and Perla and Deutsch[35] have described a gross lesion in the aorta that is distinctive. Elevated, brownish, almost transparent intimal plaques or ridges are found closely resembling the lesion of auricular endocarditis and easily separated from arteriosclerosis and syphilitic aortitis.

The histologic alterations are swelling of the fibrillar material of the intima with surrounding large cells having basophilic cytoplasm and large, vesicular nuclei with a prominent chromatin mass. Fibrin may be present on the surface. The elastic fibers are disrupted and scarring extends into the adjacent media. In other places a more diffuse inflammatory reaction occurs, polymorphonuclear leukocytes and cells with elongate nuclei being found in the intima quite similar to the lesion in the left auricle. (Fig. 9.) These changes cannot be attributed to extension of the inflammation from the aortic valve cusps as they are too far removed from them and must be considered independent lesions.

Lesions in the pulmonary artery similar to those in the aorta have been described by Paul,[37] Kugel and Epstein[38] and Gray and Aitken.[36]

In the smaller vessels numerous observers mention swelling and proliferation of the endothelium. A specific type of involvement of arterioles and capillaries has been described. There is a fibrinous exudate beneath the endothelium, at times extending through the vessel wall and often associated with hemorrhage. The vessel wall is necrotic and about the vessel collect polymorphonuclear neutrophiles and eosinophiles, large mono-

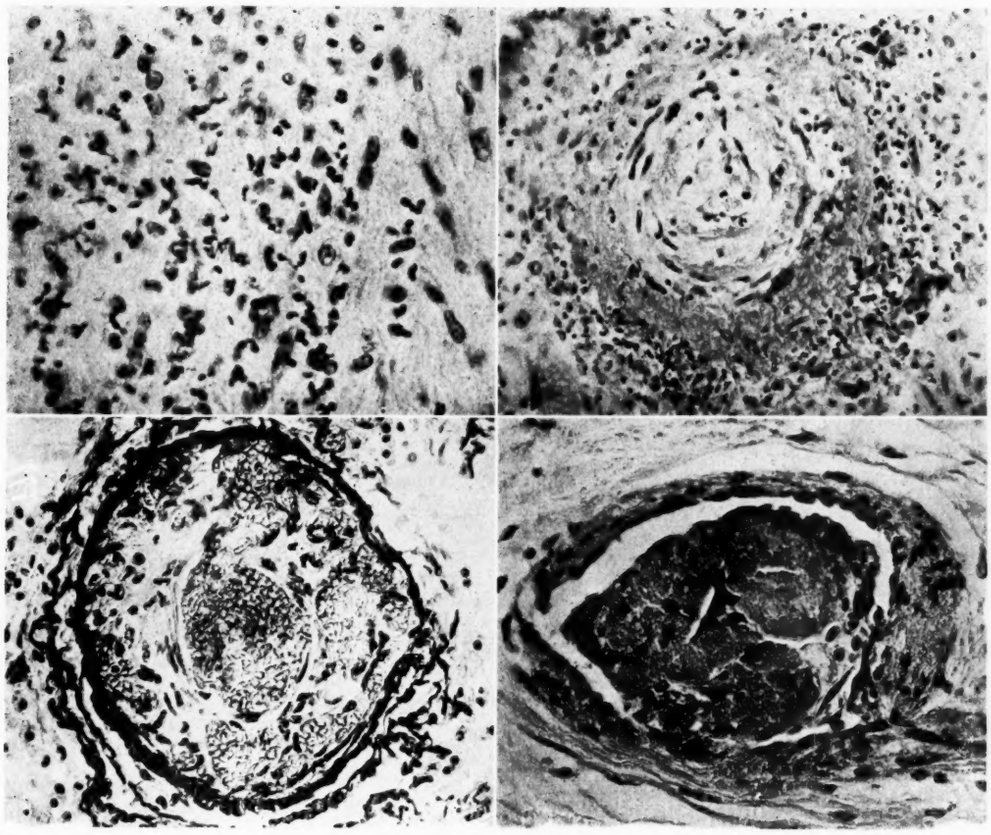

FIG. 9. Rheumatic aortitis; acute reaction similar to that seen in left auricle; polymorphonuclear leukocytes and cells with distorted nuclei.

FIG. 10. Lung: rheumatic arteritis; necrosis of vessel wall with acute inflammatory reaction.

FIG. 11. Lung: rheumatic arteritis; healed lesion with formation of new channels; elastic tissue—hematoxylin and eosin stain.

FIG. 12. Verrucous arteritis; heart.

nuclear cells and cells with distorted nuclei, similar to those seen in the auricular endocarditis. The elastica is stretched, fragmented or ruptured. Thrombi are not found. (Fig. 10.) The surrounding capillaries are greatly engorged. Healing takes place in one of two ways. When only fibrin is found, it is replaced by connective tissue and the end result simulates an obliterating endarteritis.

If hemorrhage is present with the fibrin, endothelial cells creep down and surround the extravasated blood forming new capillaries that empty into the narrowed lumen. In the affected artery, one of the new capillaries may begin in the media and penetrate through a gap in the elastica interna to communicate with the lumen; in other instances one of the new capillaries situated close to the internal elastic membrane may sweep half way around the vessel before it empties into the lumen. (Fig. 11.) The healed lesion, when there has been hemorrhage with the fibrin, closely resembles an organized and canalized thrombus, though careful study will disclose the absence of any remnant of a thrombus and no hemosiderin is to be seen. I have not observed any aneurysm formation as is so frequently found in periarteritis nodosa.

These lesions have been described in the smaller branches of the pulmonary, renal and pancreatic arteries, in the ovary and about the adrenals (Von Glahn and Pappenheimer).[39]

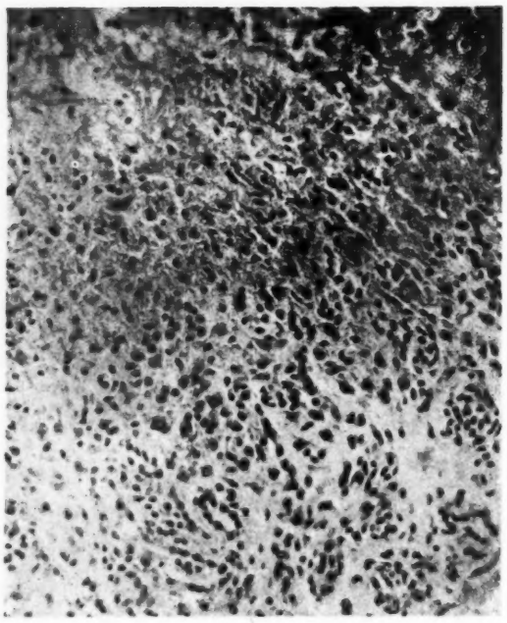

FIG. 13. Rheumatic subcutaneous nodule. A small portion of the center is shown with surrounding cellular reaction and new capillaries.

There are also lesions of the larger arteries such as the celiac axis and hepatic artery. Translucent intimal plaques are found consisting of fibrillar material infiltrated with leukocytes and large cellular components with distorted nuclei. Leukocytic infiltrations are present in the media and adventitia.[39] Holsti,[40] in a series of cases designated as arthro-nephro-cardiopathies, and also in a discussion of changes in the tonsils of a rheumatic patient, describes a verrucous arteritis. The process is apparently one of thrombosis with organization resulting in nodular or finger-like projections from the wall into the lumen. (Fig. 12.)

LUNGS

Frequent mention has been made of rheumatic pneumonia, chiefly in clinical reports. Recently descriptions have been given of a specific lung lesion (Paul,[41] Naish,[42] Fraser,[43] Eiman and Gouley,[44] Gouley,[45] and Neuberger, Geever and Rutledge[46]).

The lungs are involved to varying degrees and the gross appearance would seem to be very characteristic, as it is quite different from that of the usual types of pneumonia.

The affected portions are firm but elastic and on section the surface of such areas is smooth and deep red. The alveolar septa are infiltrated with large cells, often multinucleated, with plasma cells, lymphocytes and some polymorphonuclear leukocytes. Nodular accumulations of large cells, that resemble Aschoff nodules, are described in the interlobular septa.

The alveoli may contain a little serum with fibrin, or blood and a few neutrophiles. The alveolar lining cells are desquamating. The blood vessels are engorged. There is also described fibrinoid necrosis of the alveolar septa. The exudate in the alveoli may undergo organization with the formation of fibrous plugs. In the late stage the septa are widened by fibrous tissue and the alveolar lining cells prominent. Some of these cases have associated lesions of the arteries as outlined above.

A fibrinous pleurisy is of fairly frequent occurrence even in the absence of rheumatic pneumonia.

SUBCUTANEOUS NODULE

The subcutaneous nodule is found where bony prominences are close to the skin. The center of the nodule is composed of what appears to be swollen fragmented collagen. About this is a zone of somewhat spindle-shaped cells; at the periphery are large mononuclear cells and dilated capillaries with prominent endothelial cells.[10,18,19] (Fig. 13.)

Massell, Mote and Jones[47] have reproduced these nodules by injecting blood from the patient into the subcutaneous tissue about the elbow. For several days the area of injection was rubbed at intervals and a nodule resulted. In a few instances nodules formed following the injection of salt solution and rubbing of the area.

These induced nodules were in every way identical with the spontaneous nodules.

RHEUMATIC PERITONITIS

That the peritoneum may be involved in rheumatism has been clearly established. Localized portions appear yellowish and edematous. In addition to edema, there is an infiltration of large mononuclear cells, plasma cells and a few leukocytes. Sometimes fibrin is on the surface (Paul,[48] Wood and Eliason[49] and Rhea[50]).

RHEUMATIC NEPHRITIS

Blaisdell[51] has described changes in the kidney attributed to rheumatism. The lesion is interstitial and the glomeruli are not damaged. There are nodular collections of lymphocytes, plasma cells, a few polymorphonuclear leukocytes and indefinitely outlined cells with pale nuclei in the adventitia of the vessels. Occasionally the same types of cells are found in the media of the arterioles with degeneration of the muscle. The intima is not constantly nor characteristically involved.

JOINTS

The joint cavity contains an excess of fluid in which is a little fibrin and a few polymorphonuclear leukocytes. There is edema and hyperemia of the synovial membrane with edema of the periarticular tissues. Focal necroses in the capsule, thrombosis of the smaller arteries and cellular accumulations comparable to those of the subcutaneous and Aschoff nodules are found in the periarticular tissues (Fahr,[52] Coombs,[53] Swift[54]).

CHOREA

The brain shows little but hyperemia grossly. The histologic lesions though widely scattered are localized especially in the gray matter, the basal ganglia, brain stem and in the neighborhood of the aqueduct. There are thrombi in the smaller arteries, hemorrhages, engorgement of the vessels and proliferation of the endothelium with fat droplets in some of these cells. Perivascular and diffuse infiltrations of wandering cells, chiefly mononuclear are found; areas of softening sometimes occur. The ganglion and cortical cells show varying degenerative changes (Poynton and Holmes,[55] Greenfield and Wolfsohn,[56] Urechia and Mihalescu[57] and Castrén[58]).

Von Sántha[59] has described thrombi in the pial veins and arteries with canalization, intimal thickening and subendothelial exudate in these vessels. In the brain there is an acute endarteritis with an increase of endothelial and adventitial cells and sometimes fibrin in the vessel wall, extending out into the surrounding tissue. These vessel changes lead to focal necrosis in all parts of the cerebrum but especially in the cortex.

I am indebted to Dr. James W. Jobling, Department of Pathology, College of Physicians and Surgeons, Columbia University, for the photographs.

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Conference on Therapy

Treatment of Rheumatic Fever

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy by The Macmillan Company.

DR. HARRY GOLD: The treatment of rheumatic fever is the subject of our conference this afternoon. Dr. Robert Watson of the Rockefeller Institute will make the opening remarks.

DR. ROBERT WATSON: Rheumatic fever is a febrile disease of unknown etiology. It is an essentially chronic disease with a high tendency to recurrences, often presenting acute phases. Its clinical manifestations are numerous and varied, the chief ones being arthritis, carditis and fever.

There is no specific cure for rheumatic fever, although dramatic effects on some of the signs and symptoms of the acute phase of the disease are produced by salicylates, aminopyrine, and cinchophen or neocinchophen.

The patient who presents himself with the acute manifestations of rheumatic fever is put at rest in bed. He is given a well balanced and nourishing diet. Nursing care can be of considerable comfort to the patient at this time, particularly if he has acutely inflamed joints.

Of the antirheumatic drugs, one of the derivatives of salicylic acid is most commonly employed, either acetylsalicylic acid (aspirin), or sodium salicylate. There seems to be no essential difference between the therapeutic effects of the two. I usually give from 5 to 10 Gm. per day, the total dose being divided into six fractions, administered at four-hour intervals during the day and night. Sodium bicarbonate is given simultaneously in doses one-half of that of the salicylates. The object is to give enough salicylate completely to relieve the acute symptoms, including the joint manifestations and the fever, whenever possible. The tolerance and the requirements differ from one individual to another. A plan commonly recommended in many of the modern textbooks is to give salicylates at frequent intervals at the beginning to the point of toxicity and then, after a brief interval of interruption, to resume the drug at a lower dosage level. I see no value in the initial dosage to the point of toxicity. Doses between 5 and 10 Gm. daily usually produce the desired effects, without inducing toxic symptoms.

The drug is best tolerated after meals, and if the time for a dose happens to fall between meals, a glass of milk and crackers taken before the drug often controls much of the epigastric burning and discomfort. There seems to be a tendency for patients to develop a tolerance to the local gastric effects; they often complain of anorexia, tinnitus, nausea and occasionally vomit, during the first three or four days, but then these symptoms seem to disappear and the drug is then taken without difficulty. If nausea, vomiting, deafness or tachypnea persist, it is usually an indication of salicylism, indicating that the limit of systemic

tolerance has been exceeded. In that case the dose may be decreased, or the amount of sodium bicarbonate increased. Within limits, either of these procedures has the same effect, namely, to reduce the concentration of salicylate in the blood, since the occurrence of salicylism is related to the blood level of the drug. In those in whom vomiting occurs from other causes, the drug may be administered by rectum. Sodium salicylate is usually given in doses of 3 to 4 Gm. dissolved in 150 to 200 cc. of warm starch water three to four times a day.

For patients who cannot tolerate adequate doses of salicylates, aminopyrine may be given, although it is unwise to use it routinely because of its tendency to produce granulocytopenia. Aminopyrine is as effective as the salicylates in about one-half of the dosage of the latter. It may be given in doses of 2 to 5 Gm. daily, divided into six equal fractions, and administered in the same way as the salicylates. It causes no gastric irritation and does not produce signs or symptoms of salicylism. It is not necessary to use sodium bicarbonate with it. When the patient is taking aminopyrine, it is necessary to check the blood frequently and discontinue the drug at the first signs of leucopenia or a decrease in the granulocytes.

Cinchophen and neocinchophen are also effective in rheumatic fever, and are sometimes used in place of the salicylates. They are apparently equally as effective in doses similar to those of the salicylates, but I do not recommend them because of the danger of liver damage. I mention them only because they have been employed, and to indicate that other drugs not related chemically to salicylates are effective.

On a regimen which includes bed rest and adequate doses of salicylates, the response of most patients in the acute phase of rheumatic fever is usually dramatic; the temperature falls to a normal level within twenty-four to forty-eight hours; the joint pains subside promptly; fluid which may be present in the joints disappears within a few days; the appetite improves; the patient begins to gain weight; the systemic symptoms disappear; and the leukocytosis gradually subsides within the first week or two. The decline of the elevated sedimentation rate tends to lag, but after a week or two begins to fall toward a normal level. The sedimentation rate is probably the best single test for following the course of the disease. I usually continue salicylates for a period of two weeks after the patient is not only asymptomatic, but the leukocytosis, the elevated sedimentation rate, the fever and the electrocardiographic abnormalities have all disappeared. The dosage is then gradually reduced over a period of a week to ten days, when it is discontinued if the patient's condition remains unchanged. In the event that there is no sign of recurrence after the patient is without the drug for two weeks, he is allowed up, and the length of time he is up is gradually increased, provided the patient shows no signs of active infection. The period of convalescence and the degree of physical activity allowed, depend on the amount of cardiac damage the patient has suffered.

In a small percentage of cases, following the withdrawal of salicylates, an elevation in the sedimentation rate may occur without any other signs or symptoms of "activity," but this usually will return to normal in a very short time. In still another group all the signs and symptoms of "activity" may return, and in this event the patient is put back at bed rest and on salicylates.

DR. GOLD: A very dramatic picture has recently been painted of the effect of salicylates in acute rheumatic fever: here is a patient very ill, with high fever, and acutely painful and swollen joints; he receives 10 or 20 Gm. of sodium salicylate intravenously; in five hours he is virtually free of symptoms; in twenty-four hours he is afebrile; and in

two weeks the sedimentation time is back to normal; he does not develop heart disease. This is the kind of picture we see from Coburn's recent publications. Is there anyone here who has had similar experience?

DR. MAY G. WILSON: That is not the way the matter looks in children. I know of several studies in which the administration of large doses of salicylates intravenously made the patients feel better but the disease continued to progress.

DR. SAMUEL Z. LEVINE: The fall of the sedimentation time, like the prolongation of the prothrombin time, may have nothing to do with the cure of the disease, and is simply one of the effects of the salicylates, not specific for rheumatic fever.

DR. WATSON: At this point it might be well to say a word about the so-called "massive" dose method of the use of salicylates in the treatment of rheumatic fever. This brings up an old controversy, one that dates back to the beginning of the present century. Coburn revived this question in 1943. He believed that by means of "massive" doses, 10 Gm. daily or more, the cardiac sequelae could be prevented. The system he recommended involved the use of from 10 to 20 Gm. of sodium salicylate intravenously in 1,000 to 2,000 cc. of physiological saline daily for a period of about seven days. This was followed by a period of about three weeks in which the patient received 10 Gm. daily by mouth, administered in fractions of 1.5 Gm. and about half as much sodium bicarbonate every four hours day and night. These doses were sufficient to produce salicylate blood levels of about 35 mg. per 100 cc. of plasma. The plan was to maintain patients on this regimen until symptoms and signs of "activity" subsided, and the sedimentation time returned to normal. The treatment was resumed in the event acute symptoms and signs recurred after withdrawing salicylates. Coburn's statistics are very striking, but attempts by other workers to repeat his results have not been successful. We are back to where we were many years ago, with no proof that "massive" doses of salicylates accomplish anything more than those necessary to control the signs and symptoms. Furthermore, there seems to be no justification for the routine use of intravenous therapy. There is danger of severe toxic effects after the intravenous administration of large doses of sodium salicylate. Moreover, the blood level necessary for therapeutic results is reached sufficiently rapidly by oral doses.

DR. JANET TRAVELL: Can you not attain the same blood levels of salicylates by the oral route as by intravenous injection?

DR. GOLD: Yes, you can, but it takes longer to get there. The large intravenous injections may attain a maximum blood level in a few hours, while the usual system of oral doses attain such levels only after about twenty-four hours or longer. There is the other point that if one attempts to reach maximum levels too quickly by the oral route through the use of larger doses, vomiting results and the drug is lost. In vomiting resulting from the intravenous administration, there is no chance of losing the drug.

DR. TRAVELL: Dr. Lewis A. Conner used to order the salicylates routinely to be given by rectum.

DR. WILSON: I have used it that way and it is very satisfactory.

DR. WATSON: The patient with rheumatic polyarthritis and carditis, who develops cardiac failure, is treated in the same manner as others, in addition to the usual measures for the treatment of heart failure, namely, elevation of the head of the bed, limited fluids, restricted salt intake, digitalization and diuretics if needed. There is the belief that digitalis is contraindicated in acute rheumatic carditis. I do not share that view, and it is my experience that the drug is often beneficial. There is the fact that in

active rheumatic carditis, digitalis does not produce effects as dramatic as in cases of heart failure due to other causes, such as in cases of hypertension or inactive rheumatic heart disease. It also should be given more cautiously, since some patients with acute rheumatic carditis do not tolerate the drug very well. The xanthine diuretics are useful in some patients with heart failure due to active carditis. I have used theobromine-calcium salicylate in doses of 3 to 4 Gm. with favorable results. The mercurial diuretics are also beneficial in some of these cases, as they are in other forms of heart failure.

Thus far, I have considered chiefly those cases who respond satisfactorily, those in whom the signs and symptoms of the disease subside in a matter of a few weeks or months of treatment. There are many patients who do not respond so satisfactorily to treatment; the sedimentation rate remains elevated; the electrocardiographic changes persist; and other signs and symptoms of the disease continue on for a period of months. In these it is well to continue the salicylates. Physical activity should be restricted, although it is often not possible or necessary to keep the patient at bed rest for long periods of time such as eight to twelve months or more. Bathroom privileges and sitting in a chair do not seem to do them any harm. In these cases the treatment has to be suited to the individual case.

A word or two about some of the other drugs. Codeine and morphine are not very useful for the relief of the joint symptoms. They have to be given in such large doses as to cause drowsiness and depression in order to provide relief. Codeine is sometimes effective in controlling the precordial pain in some cases. The dangers of morphine in patients with heart failure are well known.

Sulfadiazine is effective in preventing recurrences when given continuously during the inactive phase of the disease. It is not effective during the active phase of the disease and there is experience indicating that the sulfonamides administered during the active phase, may cause exacerbation of signs and symptoms.

Penicillin is likewise ineffective in rheumatic fever. In our experience its use has no effect on the course of the disease.

As far as I know, streptomycin has not been tried. I see no reason why it should be effective, but, no doubt, it will be tried when more of it becomes available.

The question of a pericardial tap frequently arises in patients with acute rheumatic fever. To differentiate pericarditis with effusion and tamponade from a greatly dilated heart is often a difficult problem. The two are easily confused, and oftentimes, pericardial taps yield only cardiac blood. Adequate doses of salicylates given early will often prevent the development of pericardial effusion sufficient to give rise to cardiac tamponade.

Pleuritis is another very common manifestation of active rheumatic fever. It is treated as is pleuritis in any other disease, in addition to salicylate therapy. Occasionally, thoracentesis is necessary, particularly in those cases with advanced failure.

Epistaxis sometimes becomes a serious problem in rheumatic fever. Those who are prone to develop it are instructed to use a little vaseline or 1 or 2 drops of mineral oil in the nose twice a day. This simple measure often eliminates further trouble from this source. The question recently has been raised as to whether the epistaxes are due to a prolonged prothrombin time as a result of the administration of salicylates, since it has been shown that salicylates in the doses used in rheumatic fever may cause some prolongation of the prothrombin time, and in toxic doses may prolong the prothrombin time very greatly. In our own experience with a small series of patients, the prothrombin time was found to be

slightly prolonged during active rheumatic fever before salicylates were given, and changes in the prothrombin time followed more closely the course of the active rheumatic fever than the dosage of salicylates. There also is the question of whether vitamin K should be used routinely with salicylates in rheumatic fever. I do not employ it routinely, but I do use it in those patients who develop epistaxis or other hemorrhagic manifestations.

Thus far, we have said nothing about climatotherapy, the matter of moving patients to other climates for prophylaxis or treatment. I shall be glad to answer any questions that may arise in this regard during the discussion.

Finally, there is the problem of foci of infection, such as the tonsils and the teeth. I believe it is usually best to wait until the active disease has subsided before undertaking surgical measures for the removal of possible foci. The indications for these measures are the same as in an otherwise healthy individual, and not with the idea that it will influence the course of the rheumatic fever favorably. There is another point, that when we remove the tonsils or teeth from a patient who has had rheumatic fever, it is wise to give large doses of penicillin in an effort to prevent subacute bacterial endocarditis which sometimes develops in these patients after these procedures. This drug should be started a short time before the operation and continued for about forty-eight hours after.

DR. GOLD: The subject is now open for your discussion. Are there any questions?

DR. MCKEEN CATTELL: I wonder if you or Dr. Watson would enlarge on the mechanism of action of the sodium bicarbonate in reducing the blood levels of salicylates.

DR. GOLD: Dr. Watson, would you care to answer that?

DR. WATSON: It is probably due to increased renal excretion caused by the bicarbonate. There are several recent papers all published in 1946 showing that sodium bicarbonate increases urinary excretion of salicylate, namely, the one by Caravati and Cosgrove in the *Annals of Internal Medicine*, and those by Smith et al., and Lester et al., in the *Journal of Pharmacology*.

DR. CATTELL: Is the routine use of bicarbonate with salicylate for the purpose of reducing the blood level or for reducing gastric irritation?

DR. WATSON: The chief purpose is to reduce gastric irritation. It certainly relieves the epigastric burning which is apt to occur immediately after the salicylates. However, only by lowering the blood level can one control the signs and symptoms of true salicylism.

DR. CATTELL: It would seem that one really defeats one's purpose to the extent that the bicarbonate reduces the blood level of salicylate, is it not so?

DR. WATSON: That is right. However, by proper adjustment of the doses of the two drugs, one can get an effective blood level and still do away with the gastric irritation.

DR. GOLD: There is considerable controversy in the literature concerning the effect of sodium bicarbonate on the excretion of salicylates. In the well known textbook on Pharmacology by Goodman and Gilman, the statement is made that sodium bicarbonate does not hasten salicylate excretion. In relation to the blood level, there is the point made by Bradley et al. in 1936 that sodium bicarbonate slows up gastric absorption because of the rise in the pH of the solution in the stomach. The recent paper in the *Journal of the American Medical Association* by Smull, Wégria and Leland mentions two possible causes for the fall of the blood level, aside from excretion, interference with the absorption of salicylate from the intestine and increase in the extracellular fluid by the bicarbonate which leads to a decrease

in the concentration of the salicylate in the blood.

Again, as Dr. Cattell pointed out, the sodium bicarbonate tends to defeat the purpose of large doses. One might just as well give smaller doses than larger ones counteracted by sodium bicarbonate which reduces the blood level of salicylate.

DR. WALTER MODELL: Did Dr. Watson state that if adequate doses of salicylates were given, pericarditis with effusion was not likely to occur?

DR. WATSON: Yes, if the drug is started early enough.

DR. MODELL: Would this not indicate that salicylates have a specific action in preventing cardiac complications?

DR. WATSON: No. Salicylates do not seem to affect the proliferative reaction of the disease and it is this that probably causes most of the valvular damage. It is the exudative reaction which is to a large extent controlled by the salicylates.

VISITOR: Is the response of the temperature to salicylates in rheumatic fever sufficiently characteristic to use this as a means of differentiating rheumatic fever from other fevers in the absence of the characteristic joints?

DR. WATSON: The temperature response to salicylates in rheumatic fever is usually much more striking than in other types of infectious diseases, particularly in those diseases with joint manifestations such as rheumatoid arthritis, lupus erythematosus, etc.

DR. GOLD: Would it enable one to distinguish an attack of rheumatoid arthritis from one of rheumatic fever?

DR. WATSON: It would help.

DR. CATTELL: It was not clear to me how long Dr. Watson would continue the salicylates after the acute phase of the disease had subsided. Suppose the sedimentation remains elevated for six months, at what point would one discontinue the drug?

DR. WATSON: There is no fixed point. In those cases in which the course is continuous and polycyclic, one is guided by the special problems of each case. There is no harm in continuing the drug for periods of months, and we often do this.

DR. TRAVELL: In full dosage?

DR. WATSON: Yes. Once the salicylates are started, I usually continue them at the same level of dosage until the signs and symptoms return to normal. There are some exceptions in which signs of "activity" continue for periods of many months to years.

DR. TRAVELL: But what are the criteria for the cessation of therapy?

DR. WATSON: They are different in different cases. I discontinue the drugs, if there seems to be no further response.

DR. GOLD: The type of case which you described early in your discussion, Dr. Watson, was an attack of rheumatic polyarthritis, was it not?

DR. WATSON: Yes, the acute phase of rheumatic fever with carditis.

DR. GOLD: Did you intend to indicate that in such a case the salicylates produce a cure?

DR. WATSON: No, there is no evidence that salicylates cure rheumatic fever.

DR. GOLD: Do they shorten the course?

DR. WATSON: No, at the present there is no definite evidence that salicylates even shorten the course of the disease.

DR. GOLD: You believe then, that a person with an attack of rheumatic polyarthritis, with pain and swelling of the joints, fever and elevated sedimentation rate would recover just as fast whether or not salicylates are used.

DR. WATSON: This person would recover much more rapidly from the signs and symptoms if the salicylates are used than he would without them. The response of signs and symptoms is quite dramatic. But that is quite different from shortening the course of the disease for which there is no proof up

to the present time. When the drug is discontinued, in many cases the fever, the joint pains and the elevated sedimentation time return.

DR. GOLD: I take it, therefore, that you regard the salicylates as acting in rheumatic fever, in much the same way in which quinine acts in malaria. It shortens the course of an acute attack, but does not cure the disease, and there is a question whether it even shortens the course of the disease. It is a form of "suppressive" treatment.

Dr. Watson, how do Coburn's observations stand up, in which there is indication that there may be an actual cure by the salicylates?

DR. WATSON: His cases showed recurrences as did those of all other observers. The main point of Coburn's work is the prevention of cardiac sequelae, rather than that of shortening the course of the disease.

DR. GOLD: In relation to this comment of Dr. Watson's, you might be interested in this taken from Coburn's paper of 1943. This report states that of sixty-three patients used as controls, that is, having received relatively small doses of the salicylates, about 30 per cent developed cardiac involvement, whereas of thirty-eight patients who received the more intensive treatment, 10 Gm. of salicylate daily, none showed cardiac involvement. In contradistinction to this, I have here a paper published in the *Journal of the American Medical Association* by Master and Romanoff ten years previously. They gave massive doses of salicylates, doses of the same order as the intensive doses of Coburn, 8 to 12 Gm. a day or larger. There were thirty-three control cases and thirty treated with the salicylates. They found that all of the cases in both groups developed cardiac involvement, and the duration of the acute attack was practically the same in the two groups, namely, from forty-two to forty-six days. It looks to me like two groups of observers carrying out substantially the same kind of treatment, came to diametrically opposite conclusions.

DR. WATSON: That is the way the matter stands. Some groups found that the salicylates prevent the cardiac complications, and others did not. A paper was published several years ago in which most of the statistics available at that time were reviewed. I do not remember the precise figures, but patients treated with salicylates in the range of dosage used by Coburn, showed a greater percentage of cardiac complications than the untreated ones. I do not believe that Coburn followed his cases long enough to be sure of cardiac complications. The evidence of valve damage may not appear until a year or more elapses after the patient becomes clinically "inactive."

DR. GOLD: You think then, that salicylate treatment is simply for the purpose of relieving symptoms.

DR. WATSON: At the present time we have no evidence of anything more than that.

DR. GOLD: Dr. Wilson, do you agree?

DR. MAY G. WILSON: I agree.

DR. MCKEEN CATTELL: Do the persons who use large doses of salicylates in excess of those necessary to produce maximum analgesic and antipyretic actions, have any theories as to the mechanism of action of these larger doses?

DR. WATSON: Coburn's theory suggests that it interferes with an antigen-antibody interaction which is the factor giving rise to the specific reaction of the tissues characteristic of rheumatic fever.

DR. GOLD: Would you care to make any remarks on the special problems in children?

DR. WILSON: Rheumatic fever is a systemic disease characterized by injury to the mesodermal structures throughout the body, with special affinity for cardiovascular structures. It attacks the tendons, joints, synovial membranes subcutaneous tissues, the blood vessels, the viscera giving rise to hepatitis and nephritis, the nervous system,

and the heart causing myocarditis, valvulitis and pericarditis. As you know, children relatively infrequently develop arthritis; their chief manifestation of acute rheumatic "activity" is more often carditis. Salicylates lower the temperature to near normal levels in active carditis as in polyarthritis.

DR. WATSON: That is quite true. Children often tolerate fairly high doses of the salicylates.

DR. WILSON: Care must be used in children when using massive doses. There have been many fatal cases reported. You omitted chorea in your discussion. Do you not consider it one of the major manifestations of rheumatic fever?

DR. WATSON: You are correct; it should be included.

DR. WILSON: Do you not use the salicylates for chorea?

DR. WATSON: No.

DR. WILSON: We use sedatives to diminish the choreiform movements. Phenobarbital and rest in bed are sufficient in most cases. Occasionally, we use codeine or chloral hydrate. Sometimes we have to put up protection on the sides of the bed to prevent a child from falling out. Occasionally, there is difficulty in swallowing which requires special nursing attention.

The diet is important, and if the illness is protracted, as it is in many of these children, special attention is given to the well balanced diet and easily digested foods. Vitamin supplements, especially vitamin C, are desirable.

DR. WHEELER: I would like to ask Dr. Wolff a question. What is his opinion as to the rôle of rheumatic infection in the so-called Sydenham's chorea which we see on our wards.

DR. HAROLD G. WOLFF: I think practically all of them are related to rheumatic fever. Less than half of them develop carditis.

DR. WHEELER: In our medical wards, we have often made the diagnosis of Sydenham's chorea in adults without other evidence of rheumatism, and then more intensive study revealed a nervous disorder which may have been responsible for the choreal movements. I am often not entirely satisfied that these cases have rheumatism.

DR. WOLFF: A problem is presented by the adventitious movements of tension and tic, and those associated with Graves' disease, especially in adolescents. But the criteria for Sydenham's chorea are reasonably sharp, and its relation to rheumatic fever is rather close.

DR. GOLD: I do not believe you are likely to see a long standing Sydenham's chorea without elevated sedimentation time, leukocytosis or fever.

Dr. Wilson, do I understand, that if a child presents itself with an active rheumatic carditis without polyarthritis, you would apply the same regimen of salicylate therapy as for the case of polyarthritis?

DR. WILSON: Yes. I would also use digitalis for the cardiac failure when it appears during rheumatic carditis.

DR. GOLD: I am assuming, of course, from all of the discussion which we have had, that in such a case the salicylate would be continued only so long as it appears to be controlling symptoms, that it would be discontinued as soon as it becomes apparent that the drug is not adding to the general comfort of the patient, although one still needs to consider the point that the salicylates may prevent pericardial or pleural effusions which sometimes become troublesome in these cases.

Is there anyone who objects to the use of digitalis for the heart failure of active rheumatic carditis?

VISITOR: It was mentioned on rounds this morning that at a recent pediatric convention, several pediatricians from various hospitals stated that digitalis is contraindicated in the heart failure of active rheuma-

tism. It appears that we are the only pediatric service in the city of New York which uses digitalis in this condition.

DR. GOLD: Was the reason stated?

VISITOR: It is believed that digitalis produces more toxic than therapeutic effects in these cases.

DR. GOLD: That does not surprise me. It is probably related to the point which Dr. Watson made earlier in his remarks, namely, that heart failure caused by active rheumatic carditis does not usually show the striking response to digitalis seen in heart failure from other causes. A patient with active rheumatic carditis may show cardiac failure progressing, even while lying in bed and fully digitalized. It is not at all uncommon to see such patients develop edema of the legs which increases from the ankle up to the abdomen, while they are receiving full doses of digitalis. It is clear that a severe active rheumatic process may in some way counteract the therapeutic effect of digitalis. It may so damage the heart that the muscle loses its capacity for improved contraction by the drug. That does not seem to be specific for the active rheumatic process because heart failure occurring in milder forms of rheumatic carditis responds fairly well to the therapeutic action of digitalis. On the whole, however, these patients do not respond as well as others, and because the rhythm is usually a sinus tachycardia rather than auricular fibrillation, they present no satisfactory guides to the degree of digitalization. In such cases, the dose is apt to be increased in the endeavor to secure better therapeutic results, and before long toxic symptoms appear. I think this is the reason why the incidence of digitalis toxicity is so high in heart failure with rheumatic carditis. As far as the evidence goes, there is no inherent danger in the drug; in these cases it is simply a matter of not knowing quite when to discontinue or reduce the dose until signs of toxicity appear. Would you agree with that, Dr. Watson?

DR. WATSON: I think that is quite true. The electrocardiogram is one of the few guides to dosage of digitalis in these cases. Frequent tracings are of great help in detecting toxic manifestations.

DR. GOLD: There is much misunderstanding as to the use that can be made of the electrocardiogram as a guide to the dosage of digitalis in patients with rheumatic fever. Its utility here is very limited. Digitalis produces a characteristic type of RT-T change in the electrocardiogram, which is often quite different from the T-wave change resulting from the rheumatic disease itself, although there are instances in which the rheumatic disease produces a change indistinguishable from the effect of digitalis. The first problem, therefore, is that of being certain that the change is due to digitalis. But when we have answered that question, our troubles are not yet over. There still remains the question as to the significance of the change in the RT-T segment with respect to the degree of digitalization. Does the change signify that the patient has had enough digitalis, or is in need of more, or has already had too much? Here is where the electrocardiogram fails us, for in some cases a full dose of digitalis produces very little change in the RT-T segment, while in other cases only a fraction of the amount necessary to produce the full therapeutic effect is enough to produce considerable change in the RT-T segment. In the majority of cases it is safe to assume that the patient has had large enough doses of digitalis if the drug has produced fairly marked depression of the R-T segment with deep inversion of the T-wave. If sufficient improvement of the heart failure has not occurred at that point, it is unlikely that larger doses of digitalis will prove any more useful.

The P-R interval of the electrocardiogram also presents a problem in relation to digitalis. In the patient without active carditis, it is usually possible to give the full therapeutic dose of the drug to control the heart failure without significant prolongation of the P-R interval. In the patient with active carditis, however, the disease affects the A-V conduction and makes it more sensitive to the action of digitalis. In these cases, varying degrees of block may be produced by doses of digitalis which may not be sufficient to relieve the heart failure. Thus, it is that prolongation of the P-R interval which in the absence of active carditis might serve as a satisfactory indication of profound digitalization, becomes no longer useful for that purpose in the presence of active carditis.

There is, of course, the fact that the electrocardiogram serves very well in revealing toxic rhythms produced by digitalis.

Dr. Wilson: We should bear in mind that digitalis is not an antirheumatic drug, and that the disease may grow worse with heart failure increasing, even when full therapeutic doses of the drug are given. The mistake lies in increasing the dose until toxic symptoms appear in these cases.

Dr. Gold: Would you suggest perhaps that the dosage of digitalis in patients with active carditis be arranged according to some schedule without reference to immediate signs of improvement? It would involve the same principle as the schedules of treatment in syphilis. All patients would be treated by a dosage plan having the highest potentiality for improvement and lowest risk of toxicity without varying the system significantly from case to case.

Dr. Wilson: That is essentially the system I follow.

Dr. F. Homburger: I was very much interested in Dr. Watson's remarks concerning the effect of sodium ralicylate on the sedimentation test, namely, the fact that the sedimentation time returns to normal when the drug is given and becomes elevated again when the drug is discontinued. I have observed several cases of febrile conditions and cancer, in which toxic doses of sodium salicylate lower the sedimentation time to normal. There was a recent report on this subject. Since this is so, I wonder whether, once salicylate treatment is started, the sedimentation rate does not lose its value as a guide to the presence of the rheumatic infection.

Dr. Watson: It is well known that the sedimentation rate is not specific. It is also clear that when the sedimentation time returns to normal during the use of the salicylates, it may rise again when the drug is discontinued, and, therefore, the drug does not cure the disease. Even though it is a poor index at best, we do not have any better one. The white blood cell count is not nearly as useful a guide.

Dr. Gold: Are there any other questions?

Dr. Morris Pearlmutter: What about the value of the anti-streptolysin titer as a guide to rheumatic activity?

Dr. Watson: It does not follow the course of the disease process.

Dr. Pearlmutter: Does it not represent "activity" when it is markedly elevated?

Dr. Watson: Oh, no!

Dr. Gold: Dr. Wilson, what about the anti-streptolysin titer?

Dr. Wilson: I agree that it has little value. It only means that the patient at some time had a streptococcic infection.

Dr. Pearlmutter: Would that also be true if there were a sudden change in the level of the titer, let us say, a sudden rise from 200 to 800 units per cc.?

Dr. Wilson: No matter what the change was. All it reflects is a streptococcic infection. It has nothing to do with rheumatic fever, in my opinion.

Dr. Gold: Even though the anti-streptolysin titer may have no meaning with

respect to the specific cause of rheumatic fever, there is the observation that a high titer is more apt to occur in rheumatic polyarthritis than in, for example, rheumatoid arthritis. Would the finding of a high titer in a case in which the problem of a differential diagnosis exists, prove helpful in arriving at a decision?

DR. WILSON: No, there are several studies showing that in rheumatic fever the titer is not more often elevated than in non-rheumatic subjects experiencing streptococcal infections.

DR. SEYMOUR RINZLER: In relation to the congestive heart failure occurring in these cases, has Dr. Watson any experience with the mercurial diuretics used alone for the control of the failure?

DR. WATSON: Our patients in this condition are routinely digitalized. I do not recall having used the mercurial diuretics alone.

DR. OVIDIO MIQUEL: There is an article in the *New England Journal of Medicine*, in November 1945, on the treatment of rheumatic fever with a calcium double salt of benzoic acid and succinic acid benzyl ester, which suggests that it may be more effective than salicylates.

DR. WATSON: That is the paper by Gubner and Szucs. It is the only report on this subject that I know. I have no experience with it. I know of no one who has corroborated it.

DR. GOLD: Is there anyone here familiar with that work?

DR. WATSON: It is possible that benzoic acid might have a slight effect in relieving symptoms.

DR. GOLD: The authors stated their belief that the benzoic acid component played little part in it since the total daily dose of the acid was less than 2 Gm. The compound was given in daily doses of from 4 to 5.3 Gm. They attributed its efficacy to the succinic acid fraction, and postulated that since this compound is a very active reducing substance, it may help to maintain cytochrome in a reduced form and prevent inactivation of other respiratory enzymes. They take the position that there is evidence for a widespread oxidative inactivation of enzymes in rheumatic fever. The results they described are dramatic, but then, the results of the treatment of rheumatic fever present such strange contrasts in the hands of different observers.

DR. WATSON: It certainly does.

VISITOR: We see many patients who seem to feel quite well two months after an attack of rheumatic fever, but the sedimentation time remains elevated. What should we do in regard to their physical activity?

DR. WATSON: I believe their physical activity should be restricted until evidence is obtained from the sedimentation rate, and from other guides such as frequent electrocardiograms, that the disease has subsided.

DR. GOLD: I wonder if Dr. Wilson would enlarge a bit on the problem of rest in bed, when to start and when to stop bed rest.

DR. WILSON: The general rule is that the child with active rheumatism belongs in bed. It is quite a problem, however, to decide when to let them out of bed. In general, this may be done when all constitutional signs or symptoms have subsided, fever, leukocytosis, elevated sedimentation rate and signs of diminished cardiac reserve. In the case of those who receive the salicylates, a week or more should elapse without the drug before the child is allowed up and about, since the salicylates may suppress the evidence of the active disease and symptoms and signs may return when the drug is discontinued.

The child who is normal in every respect except for the elevated sedimentation time, presents a special problem. I usually let them up and about, and in the course of many years of experience with this practice, I have had no reason for changing it. A thorough search in these cases sometimes

discloses an enlarged lymph node, a postnasal discharge, sinusitis or some other cause for the elevated sedimentation time.

VISITOR: If a child has intermittent mild joint pains, but without fever or leukocytosis, do you keep such a one in bed?

DR. WILSON: Such a child belongs in bed during the periods when there are joint pains.

DR. CATTELL: How long is the period of bed rest in the average cases?

DR. WILSON: It varies widely. I know patients with severe carditis in whom the period of bed rest required was only a matter of weeks, and others who had to be kept in bed for a year or two.

DR. CHARLES WHEELER: Dr. Wilson, it has recently been fashionable to question the value of bed rest. Is there any doubt in your mind that it is necessary?

DR. WILSON: As long as the rheumatic process is active, the child should stay in bed. It is my experience that when these children are not under proper supervision and are allowed up and about, they develop increasing symptoms of heart failure.

DR. CATTELL: Do you encounter any complications as a result of the child being in bed?

DR. WILSON: Do you mean psychiatric troubles, difficulties in adjustment?

DR. GOLD: Phlebitis, or pulmonary complications.

DR. WILSON: No, I have never observed that in any child that I can recall.

DR. GOLD: In the matter of keeping the child in bed, it seems to me necessary to decide the question, which is more harmful, to be jumping about in bed, or jumping about in the room. It is not easy to keep them at rest in bed.

DR. WILSON: I think good nursing takes care of that.

DR. GOLD: Would Dr. Wilson say a word about the matter of changes in climate in the management of rheumatic fever?

DR. WILSON: The idea in a change in climate is to prevent respiratory infections which are considered to bear some relationship to rheumatic recurrences. It is desirable to have the patient in a section of the country where respiratory infections are infrequent, where the temperature is mild, and does not show wide fluctuations. If the parents can conveniently take up permanent residence in such an area, it is well to do so. The evidence of its value, however, is not sufficiently strong to justify undue financial hardships in making this change. A change in climate for only a month or two is not advisable. In the case of those families who can manage just as well living in Tucson, Arizona, as in New York City, I sometimes recommend that they move to Tucson. A place like Miami, Florida, does not seem to offer very much. There many of the dwellings are not constructed for all-year round residence; there may be no central heating; and there is a long rainy season. It is the general experience that rheumatic recurrences are as likely to occur there as in New York City.

DR. GOLD: I believe that this question has already been answered in one form or another, but I am still troubled with the possibility of a misunderstanding. Assume a patient ill in bed with active rheumatic carditis and a high fever, and when you give him moderate doses of the salicylates, he shows considerable intolerance to them; he develops profuse sweating which keeps his clothes constantly soaked, his stomach is upset, and there is an unpleasant ringing in the ears. It is true that the temperature is lowered a degree or two, but there appears to be so much unpleasantness connected with it. Would you object to discontinuing the salicylates in such a patient?

DR. WATSON: I would switch to aminopyrine.

DR. GOLD: Suppose the aminopyrine succeeded in lowering the temperature a de-

gree or two, but the patient continued to look and feel substantially as ill as he did before. Would you be inclined to continue the drug because of this effect on the fever even though there seemed to be no other beneficial effect apparent? So often we see these drugs continued for long periods of time without signs of making the patient feel better, and sometimes making them feel worse, even though the general range of the temperature is lower.

DR. WATSON: I think that lowering the temperature two degrees might be of some benefit.

DR. CATTELL: As I understand Dr. Gold's question, would it be desirable to try to obtain that result if the patient is reasonably happy without the drug?

DR. WATSON: We should not continue any of these drugs if after a reasonable trial it is clear that the signs and symptoms are not improving, for there is no good evidence that the basic course of the disease is influenced by them.

DR. GOLD: Therefore, if the patient does not begin to feel better, we should discontinue them, and let the disease run its natural course.

DR. WATSON: I agree with that; if the drug is given a sufficiently long trial in adequate dosage, and provided there are no changes in the patient's condition to indicate he was worse after discontinuing the drug. Otherwise, the drug should be started again.

VISITOR: Could we have a little more discussion of the use of the sulfonamides in prophylaxis? Dr. Watson said they were valuable for prevention.

DR. DAVID P. BARR: It is not clear to me why patients with acute rheumatic fever who have improved but are not yet entirely well should suffer a recrudescence of the disease after the sulfonamides. Is there any reason for that?

DR. WATSON: I know of none.

DR. BARR: I believe the evidence is about equally strong for penicillin producing a recrudescence.

DR. WATSON: The report by Foster in the Air Force study showed that patients with rheumatic fever did not take penicillin well and that the disease was aggravated. In our own study with relatively few cases, there seemed to be no difference.

VISITOR: Will any of the sulfonamides do?

DR. WATSON: I do not know of any experience with sulfathiazole or sulfapyridine.

VISITOR: Is there any danger in the patient becoming drug-fast as the result of the prophylactic use of sulfa in rheumatism so that it would fail to act effectively when the need for it arises in connection with some other disease?

DR. WATSON: It is not the patient who becomes drug-fast but the organism. The drug is not effective against drug-fast organisms.

DR. GOLD: Dr. Wilson, what are your views on sulfa prophylaxis of rheumatism?

DR. MAY G. WILSON: I do not believe there is any satisfactory evidence that the sulfa drugs prevent rheumatic recurrences. There are several studies which indicate that a streptococcal infection is one of the factors responsible for recurrence of rheumatic fever, and it was hoped that by preventing these infections, the recurrence of the rheumatism might be prevented. Unfortunately, however, the studies were not so planned as to make an evaluation possible. The numerous variables were not taken into consideration. It has been shown that the risk of recurrence varies with the age of the child and the time that has elapsed since the last attack. These factors were not considered in the studies on sulfa prophylaxis. Also, they failed to examine the problem by the alternate case method which tends to eliminate bias in selection.

DR. WATSON: I disagree with Dr. Wilson in regard to the value of sulfa prophylaxis.

It is true that some of the studies were not very well controlled, but Dr. Kuttner's in particular, have been about as well controlled as possible in such a problem; they took into consideration the factor of age and number of previous attacks. The difference between the results in the control and treated groups was quite significant.

DR. WILSON: I cannot agree with Dr. Watson's view that Dr. Kuttner's cases were adequately controlled. Although she did try to match cases by age, the alternate case method necessary to eliminate bias in selection was not used. The factor of the length of time elapsing since a previous attack of rheumatism was not satisfactorily applied. This is of the greatest importance. In estimating the natural risk of recurrence, we found that the person who has had an attack during the previous year, has three times as great a chance of a recurrence as the one who has not had an attack for a year. When we applied out methods of analysis to Dr. Kuttner's control group of patients, we learned that there were far more recurrences there than were to be expected. It was evidently, therefore, a biased group, and hence the fact that there were fewer recurrences in her treated group cannot be accepted as representing a significant effect of the drug.

DR. BARR: Is the danger in the use of sulfadiazine a factor in restraining Dr. Wilson from using it in the prophylaxis of rheumatism.

DR. WILSON: No, there simply is no evidence that convinces me that the sulfa drugs have prevented recurrences. In all the published studies in civilian life, I find the same difficulty in evaluating the results. Until a properly controlled study is done which demonstrates that sulfa drugs can prevent rheumatic recurrences, I see no justification for this routine practice. At the present time, its use should be limited to experimental investigations.

DR. GOLD: I think that Dr. Wilson's point about controls is a very important one, namely, the fact that the time which has elapsed since the last attack of rheumatism is a factor determining the likelihood of a recurrence. Clearly, if the group used as controls all had an attack last year, and the sulfa-treated groups have gone two years without an attack at the time that they were put into the study, the results might show a much higher incidence of recurrence in the controls than in the treated cases. But these results would be deceptive. According to Dr. Wilson, that is what would be expected in two such groups even if both were untreated with sulfa. I might add that Dr. Messeloff made a serious attempt to test the value of sulfa prophylaxis in our childrens' cardiac clinics, and was unable to detect any difference between treated and untreated cases.

DR. SAMUEL Z. LEVINE: There is clearly an unsettled controversy regarding the effectiveness of sulfonamide therapy as a prophylactic measure in rheumatism. The bulk of opinion favors it. I have spoken to Dr. Paul and a number of persons who have used sulfonamide therapy as a prophylactic procedure, and they all appear to be enthusiastic about it. Dr. Wilson's objection on the grounds of inadequate controls, I think, leaves the evidence inconclusive.

DR. CATTELL: I wonder how the proponents of the prophylactic use of sulfonamides explain the failure of the drug to benefit the disease after it has started.

DR. WATSON: It is a fact that the drug is of no benefit after the disease has started, and during the active stage it may aggravate the disease.

DR. LEVINE: Dr. Coburn once told me that if you give the sulfonamides to a patient with active rheumatic fever, you are almost signing his death warrant. I think that statement is a bit strong. I do not know whether he still holds that view. I asked him

specifically whether he would give sulfonamides to a patient with pneumococcal pneumonia if he also had rheumatic fever. He said no at that time. I do not share that attitude. I do not know whether or not he has changed his.

DR. JOHN E. DEITRICK: If sulfonamide is so dangerous during the active stage of the disease, how long should one wait after an attack of rheumatic fever, before one may safely start the prophylactic therapy?

DR. GOLD: Would Dr. Watson answer that?

DR. WATSON: I think it is pretty safe to start it as soon as all signs and symptoms of active infection disappear. The sedimentation rate is perhaps the most sensitive guide. The patient should be afebrile.

DR. DEITRICK: In some cases that may mean a delay of six months or a year before the prophylactic treatment is started.

DR. WATSON: I know that Dr. Dodge has given it to patients who still had a low grade rheumatic "activity" without ill effects. Some, however, will suffer an exacerbation if the sulfonamide is given in the active stage.

DR. GOLD: What dosage of sulfa do you use for prophylaxis, 1 or 2 Gm. daily throughout the school year in children?

DR. WATSON: Usually 1 Gm. The Navy undertook a large program of sulfa prophylaxis. The incidence of streptococcal infections and meningitis was greatly reduced, and the incidence of rheumatic fever was correspondingly diminished until sulfadiazine-fast strains of streptococci appeared when the rates of streptococcal infections and rheumatic fever promptly increased again. The Air Force of the Army tried it with the same general results. Sulfadiazine is undoubtedly the best of the drugs for this purpose, although I think that sulfanilamide was chiefly used in the civilian studies.

DR. GOLD: What proportion of patients develop toxic symptoms as the result of this treatment?

DR. WATSON: It varies a great deal among the different studies, from less than 1 per cent in some to as high as 10 or 20 per cent of the cases in others. As far as I know, there has only been one death reported in civilian practice. In the Navy there were a few deaths, the exact number I do not know, but I am sure the incidence of toxic reactions was very low and, of course, the death rate was extremely low.

DR. GOLD: I have a paper here published in the *Journal of the American Medical Association* in 1940 on the treatment of rheumatic fever. All of the following suggestions for treatment are offered: streptococcus vaccine by intravenous injection, typhoid vaccine by intravenous injection, antistreptococcus serum, iron, potassium arsenite and prophylactic vaccination against recurrence. Dr. Watson, would you use any of these in your regimen for treatment?

DR. WATSON: No, I do not think I would.

DR. GOLD: We may now summarize the chief points which were discussed in the conference this afternoon. Rheumatic fever is a chronic febrile disease involving the mesodermal structures of the body. It shows acute phases and frequent recurrences. There are numerous clinical varieties depending on the structures which are predominantly involved, the chief ones being polyarthritis, carditis and chorea. The form with polyarthritis is most common in adults, and with carditis, most common in children.

There is no specific cure, but the salicylates play an important part in its treatment. There is an unsettled controversy concerning their dosage, and the question as to whether they act merely to relieve symptoms or alter the basic development of the disease. The consensus appears to be that the salicylates are "suppressive" and not curative, in much the same sense as quinine is "suppressive" in malaria. In an acute attack, under suitable doses, pain is promptly relieved, fever subsides, effusions

into joints and other cavities diminish, and the blood sedimentation time may return to normal. However, when the drug is discontinued, the signs and symptoms reappear, showing in this respect the same tendencies as in the untreated case. The "acute attack" should be distinguished from the entire "disease"; there appears to be no proof that the course of the "disease" is shortened by the salicylates. The recent revival of the belief that massive doses of salicylates given intravenously, beyond those necessary to control signs and symptoms, may prevent the development of heart disease, has not been confirmed.

Aminopyrine and cinchophen may be employed for the same purpose in patients who cannot tolerate salicylates, although their inherent toxicity is greater and are, accordingly, not advisable for routine use.

Sodium bicarbonate may be given with the salicylates to relieve gastric distress. The old controversy concerning its effect on the blood level of salicylate and the excretion of salicylate seems now to be settled by the more recent studies which are in accord in showing that the blood level of salicylate is lowered and the urinary excretion is increased by sodium bicarbonate. This fact, on the one hand, tends to diminish the efficacy of the salicylate, but may, on the other hand, be applied to the treatment of salicylate poisoning.

The details of systems of dosage for the salicylates and the other antirheumatic drugs were discussed.

The much debated question of digitalis in heart failure caused by rheumatic carditis was explored. Opinion is still sharply divided; there are those who believe that it does more harm than good, and those who believe it should be used routinely. There seems to be little doubt that the therapeutic response to digitalis in these cases is quite limited. It was suggested that in active carditis, digitalis be used in accordance with a schedule of dosage with the greatest potentiality for therapeutic effects and least likelihood of toxic effects, without change in doses in relation to the immediate therapeutic results in any particular case, in much the same way as the arsenicals are used in the treatment of syphilis. This would prevent the increase in dose to the point of toxicity as is so often the practice.

The controversy concerning the prophylactic value of sulfadiazine received considerable attention, there being those who use 1 Gm. daily throughout the school year to prevent recurrences, and those who regard this practice without sufficient proof of value. The numerous control factors which have to be taken into account in a study of the value of drugs in rheumatic fever were described.

Many other points of interest were discussed, such as the danger of the pericardial tap, the use of vitamin K to control epistaxis, the value of bed rest and the factors determining the duration of bed rest, the value of a change in climate to prevent the recurrence of active rheumatism, the use of the electrocardiogram as a guide to digitalis action in rheumatic fever and the anti-streptolysin titer as a guide to rheumatic activity.

Clinico-pathological Conference

Hypertension and Renal Failure*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, D. D., a nineteen-year white married housewife, entered the Barnes Hospital on July 30, 1946, complaining of fatigue, headache, vomiting, and shortness of breath. The family history was non-contributory. The patient had not had scarlet fever, rheumatic fever, frequent sore throats or other serious illnesses. Her health had been excellent until the birth of her only child seventeen months prior to admission. The pregnancy had apparently been entirely normal and the delivery and puerperium were uneventful. Her habits were good and her diet adequate; for years she had been very fond of salt and had drunk large amounts of water.

One month after the birth of her child the patient developed increasing ease of fatigability. She consulted a physician who examined her and told her that her blood pressure and urine were normal. Two months later she began to complain of frontal headaches which were often associated with nausea and vomiting. They continued to recur about three times a week and gained in intensity, but were usually controlled by medication. The headaches and weakness continued during the following year. Five months before entry the patient again consulted her family physician; he examined her urine and found white blood cells but no red cells or casts. The red blood cell count was reported as 3,200,000.

Three months prior to admission, the patient had severe diarrhea for a few days. Shortly thereafter, a red, raised, pruritic, discrete eruption appeared transiently on the extremities. At that time, her systolic blood pressure was recorded as 110 mm. of mercury. Subsequently "black and blue spots" developed on her extremities and these continued to appear. Shortly before admission she developed shortness of breath at night which was relieved when she sat up. Her systolic blood pressure rose to 220 mm. of mercury. Because of dull epigastric pain, headache, vomiting and shortness of breath she was admitted to the hospital.

At the time of entry, the patient's temperature was 36.9°c., pulse 110, respirations 22, and blood pressure 200/140. She was acutely ill and appeared much older than her stated age. She was able to lie in bed comfortably using only one pillow; she answered questions slowly and with difficulty. There was a brown discoloration of the skin of the face and palms but none of the mucous membranes. Over the arms and legs ecchymoses of various sizes were seen. The eyes were prominent and staring, and the palpebral fissures were widened. Two petechial spots were present in the conjunctivae. The pupils reacted normally. There was marked bilateral papilledema,

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and exudates and hemorrhages were seen in both fundi. The arterioles were narrow and tortuous. Examination of the upper respiratory tract was negative. The buccal mucous membrane was pale. The breath was not uremic. Arterial pulsations in the neck were prominent. The lungs were clear. The entire precordium heaved with each heart beat. A visible impulse was seen in the fifth left interspace in the anterior axillary line, and at the apex there was a soft systolic thrill and a grade III systolic murmur. A diastolic gallop rhythm was audible. The aortic second sound was accentuated. The liver edge was palpable 6 cm. below the right costal margin; the edge was sharp and tender. There was tenderness also in the epigastrium. The spleen was palpable 3 cm. below the costal margin. Pelvic examination revealed nothing abnormal. There was no edema. The neurological examination revealed no abnormalities.

The laboratory studies were as follows: Blood count: red cells, 2,700,000; hemoglobin, 8.5 gm.; white cells, 13,300; differential count: basophiles, 1 per cent; segmented forms, 75 per cent; lymphocytes, 19 per cent; monocytes, 5 per cent. Urinalysis: albumin, +++; casts, 0; sediment, occasional red blood cell per high power field. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 90 mg. per cent; chlorides, 82 meq/liter; total proteins, 5.8 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 2.7 Gm. per cent; CO_2 combining power, 41.5 vol. per cent; calcium, 7.5 mg. per cent; phosphorus, 14 mg. per cent. Phenolsulfonphthalein test: no dye excreted in one hour. Circulation time (decholin): 15 seconds. Venous pressure: 80 mm. NaCl. Antifibrinolysin test: negative. Aschoff-Zondek test: negative. Electrocardiogram: T wave isoelectric in lead I. Interpretation: myocardial damage. Roentgenogram of the chest: "Heart and aorta are within normal limits. The lung parenchyma is clear."

On admission, the patient was given 1.2 mg. of digitoxin orally and one liter each of $\frac{1}{6}$ molar sodium lactate solution and 5 per cent glucose in water intravenously. She also received 500 cc. of red cell residue. She became quite drowsy and developed Cheyne-Stokes respirations. On auscultation crepitant râles were heard at both lung bases. The patient vomited frequently. During her first week in the hospital no other important changes occurred.

The patient then had a clonic convulsion which was controlled with intravenous magnesium sulfate. Subsequently she had similar convulsions repeatedly. The blood non-protein nitrogen had risen to 148 mg. per cent; the chlorides had fallen to 71 meq/liter and the CO_2 combining power was 45.2 volumes per cent. The red blood cell count was 1,670,000. The breath became uriniferous. Drowsiness increased and there was occasional muscle twitching. At the end of the second hospital week sacral edema appeared. The blood chlorides had continued to fall, reaching a level of 55 meq/liter and the non-protein nitrogen was 178 mg. per cent. Supportive treatment with 5 per cent glucose and $\frac{1}{6}$ molar lactate was continued, but during the third week the blood chlorides were only 49 meq/liter; thereafter they remained at levels of that order. The venous pressure, which had been normal, rose to 235 mm. NaCl. Edema of the legs and face appeared and a pericardial friction rub was heard at the apex. Stupor, increased respiratory difficulty and intractable cardiac failure were terminal events. At no time was the temperature elevated.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: The case which we are to discuss presents a puzzling diagnostic problem. This nineteen-year old

woman had an apparently negative past history and a seemingly normal pregnancy, delivery and puerperium. One month after the birth of her child, she began to have symptoms of the disease which led to her death about fifteen months later. Dr. Schroeder, would you suggest a diagnosis.

DR. HENRY A. SCHROEDER: Chronic glomerulonephritis comes to mind first but there are several facts against that diagnosis. The patient's symptoms appeared at a time when her urine was said to have been negative and her blood pressure normal. Such a sequence of events is unusual.

DR. ALEXANDER: I should like to make an addition to the record. In the protocol it is stated that when the patient first became ill and consulted her physician, he told her that her blood pressure was normal; actually, it was 136/90. I think this information is important. It is your opinion then, Dr. Schroeder, that this patient probably had chronic glomerulonephritis?

DR. SCHROEDER: Yes, but I cannot explain the normal urine at the time when she first became ill.

DR. EDWARD MASSIE: I believe the history, findings and course are compatible with chronic pyelonephritis. A normal urine, except for a low specific gravity, may be found in chronic pyelonephritis, even in the terminal stages; I agree with Dr. Schroeder that in glomerulonephritis the urinary findings should be abnormal. In nephrosclerosis, the urinary findings are also abnormal.

DR. ALEXANDER: And if pyelonephritis were responsible for the patient's hypertension, do you believe both kidneys were involved?

DR. MASSIE: They may have been. It should be pointed out, however, that unilateral pyelonephritis can give rise to hypertension, which in turn may lead to arteriolar nephrosclerosis.

DR. ALEXANDER: Would you estimate the duration of the pyelonephritic process necessary to produce hypertension of the degree recorded in this case? Do you believe the pyelonephritis antedated her pregnancy?

DR. MASSIE: The pyelonephritis could have had its onset in pregnancy or immediately thereafter. It may be associated with rapidly developing hypertension.

DR. ALEXANDER: Are there any other suggestions?

DR. HAROLD A. BULGER: Rather than chronic pyelonephritis, I believe the patient may have had primary vascular disease.

DR. ALEXANDER: In other words, you would identify this process as arteriolar nephrosclerosis or malignant hypertension. In the history there is the statement that she was very fond of salt and drank a great deal of water. Has that fact any relevance?

DR. W. BARRY WOOD, JR.: I think it is very important and suggests that the patient's renal function was probably poor in that her kidneys were unable to secrete a concentrated urine. She apparently was forced to ingest large amounts of water in order to excrete sufficient urine to clear the blood of nitrogenous products. The polydipsia suggests that the patient had renal disease before she became pregnant.

The craving for salt and the very low serum chloride noted in the hospital bring to mind two cases that Dr. George Thorn reported in 1944.[1] Both patients entered the hospital with the symptoms of Addison's disease but were shown later to have chronic glomerulonephritis; the diagnosis was confirmed at autopsy in each case. Thorn termed the syndrome, "salt losing nephritis." Normally the adrenal cortex stimulates the reabsorption of sodium chloride from the renal tubules. In Addison's disease, the adrenal cortex fails to function, reabsorption does not take place and sodium chloride is excreted in excessive amounts. In "salt losing nephritis," the difficulty is not in the adrenal cortex but in the renal

tubules; the end result is the same in that salt is not properly reabsorbed and is thus lost in the urine. Thorn points out that while Addison's disease may be simulated clinically, "salt losing nephritis" will not respond to adrenal cortical extracts because of the site of the pathologic lesion.

DR. ALEXANDER: Dr. Allen, will you comment on the relationship of the patient's pregnancy to the underlying disease.

DR. WILLARD M. ALLEN: First of all, if this patient had had chronic glomerulonephritis, I think it very unlikely that she would have died a year and a half after her pregnancy without having had complications during her pregnancy. It is well known that chronic glomerulonephritis is reflected in pregnancy by hypertension which appears quite early; fetal death in utero at about six or seven months is not uncommon. This patient apparently went through her pregnancy without any difficulty. One month postpartum her diastolic pressure was 90 mm. of mercury. Certainly such a diastolic blood pressure is distinctly abnormal in an apparently healthy young girl of nineteen, but it does not afford much assistance in the problem of deciding whether this girl had chronic glomerulonephritis. We often see patients with chronic glomerulonephritis who have a blood pressure of this order at the beginning of pregnancy; it may rise gradually during the course of the pregnancy and even though such patients may lose the fetus in utero, they may have a blood pressure of only 135/90 four weeks after delivery.

The other suggestion which has been made, i.e., chronic pyelonephritis, may be commented on a little more extensively. In the practice of obstetrics, it is not uncommon to see a patient, who has an episode of acute pyelonephritis in pregnancy, go to term without developing any sign of toxemia. Recently we had a patient on our service who had been seen in the obstetric clinic in the seventh month of pregnancy with frank hematuria. She was seen in consultation by the urologists in regard to the possibility of a renal stone but that diagnosis was not established. Her systolic blood pressure was normal; the diastolic pressure was 90 mm. of mercury. The medical student, to whom the patient was assigned in the clinic, did a phenolsulfonphthalein test and drew blood for a non-protein nitrogen determination. Unfortunately, the patient left the clinic and was not seen after the laboratory findings were reported. When she was admitted to the hospital two weeks later, the fetus was non-viable; her blood pressure was unchanged. In checking the clinic record, it was found that the phenolsulfonphthalein excretion determined two weeks before had been zero and the non-protein nitrogen had been 100 mg. per cent. Her urine showed only red blood cells in the sediment. The patient died two weeks after entry in uremia; terminally her blood pressure had risen to much higher levels. At autopsy, she had chronic pyelonephritis of long duration.

Thus, in the case we are discussing today, the relatively unimpressive past history does not rule out pyelonephritis. We are told the patient did have white blood cells in the urine; this finding points to pyelonephritis. If I had to choose between chronic glomerulonephritis and chronic pyelonephritis, I would choose the latter, particularly if I believed that the patient's course had been deleteriously effected by pregnancy.

DR. ALEXANDER: Would you consider a third diagnosis, that of essential hypertension following toxemia of pregnancy?

DR. ALLEN: Although it is true that patients who develop severe preclampsia may have residual hypertension, I am not aware of ever having seen such a patient die of malignant hypertension only a year and a half later.

DR. PALMER H. FUTCHER: From reading Goldring and Chasis's book on hypertension, Dr. Allen, I gained the impression that they believe that pregnancy has very little influence on the course of chronic glomerulonephritis and that patients with chronic glomerulonephritis who became pregnant and develop toxemia do not fare any less well than other toxemia patients. Would you discuss further your views in regard to the effect of pregnancy on the course of chronic glomerulonephritis?

DR. ALLEN: I do not think that one can say pregnancy has an adverse effect on that disease any more than he can say it has an adverse effect on the course of heart disease. In general, it is believed that chronic glomerulonephritis does effect pregnancy. This seems particularly true in patients who have diastolic hypertension and albuminuria at the beginning of pregnancy. Such patients are most apt to develop severe complications. On the other hand, patients with elevated diastolic blood pressure but with no albuminuria may do quite well and are statistically more likely to go through pregnancy uneventfully. Successive pregnancies are apt to be very detrimental, however, and severe toxemia and fetal death are common.

DR. ALEXANDER: Dr. Wood brought out a very impressive feature in this case, namely, the hypochloremia. Dr. Futcher, would you comment on this finding?[2]

DR. FUTCHER: From Gamble's data, it is known that the serum sodium is normally higher by 15–20 meq/liter than the sum of the serum chloride and bicarbonate fractions. In this case, the total of the chlorides and bicarbonate indicates a low serum sodium; the CO_2 combining power was only slightly depressed and did not reflect severe acidosis; on the other hand, the chloride was very low. In kidney disease low values for the serum sodium and chloride can be explained in two ways. First, if the kidney is unable to make ammonia by means of which a portion of the waste acids are excreted, fixed base must be used. Second, loss of sodium chloride may be due to the mechanism to which Dr. Wood referred; that is, the specific inability of the tubules to reabsorb sodium chloride from the glomerular filtrate. In this case, I would be inclined to explain the low sodium by the second factor, especially since the CO_2 combining power was not markedly depressed. The elevation of phosphorus, of course, points to retention of inorganic acids and speaks for acidosis.

DR. ALEXANDER: One other feature of this case was the presence of petechiae for many weeks prior to the patient's death. Are there any comments in regard to these lesions?

DR. SCHROEDER: The occurrence of petechiae is quite consistent with advanced renal disease. They are seen particularly when there is nitrogen retention, and the fact that the patient had petechiae for such a long period of time strongly suggests that she had nitrogen retention at least several months prior to entry, and possibly at the time when the anemia was discovered.

DR. LEO J. WADE: Dr. Alexander, I believe this patient could have had glomerulonephritis with a normal blood pressure which rose only in the terminal phase of the disease.

DR. ALEXANDER: Against that postulation is the fact that the patient had such advanced hypertensive neuroretinopathy.

DR. WADE: Is it equally likely that excessive salt loss could occur in any one of the three diseases we are discussing?

DR. WOOD: The patients whom Dr. Thorn reported had chronic glomerulonephritis, but the phenomenon does occur to a lesser extent in pyelonephritis and nephrosclerosis. Dr. John Peters has recorded similar blood chemical findings in both chronic pyelonephritis and malignant nephrosclerosis.

DR. ALEXANDER: Although there is not complete unanimity in regard to the diagnosis, the staff seems to favor a diagnosis of chronic glomerulonephritis. Chronic pyelonephritis and malignant nephrosclerosis would appear to be less likely possibilities.

Clinical Diagnosis: Chronic glomerulonephritis and uremia.

PATHOLOGICAL DISCUSSION

DR. ROBERT A. MOORE: The three major diseases which may give rise to the clinical picture observed in this patient were discussed: malignant nephrosclerosis, chronic glomerulonephritis and chronic pyelonephritis. It may be profitable to consider the features which the kidney may exhibit on gross examination which might point to the correct diagnosis. In nephrosclerosis, the surface of the kidney may be either uniformly finely granular or it may be smooth. In addition, in the malignant phase, there will be petechiae throughout the surface of the kidney and to a lesser extent in the substance of the cortex. In glomerulonephritis, the surface of the kidney is nodular but irregularly nodular; this is in contrast with the uniform character of the nodularity in nephrosclerosis. In pyelonephritis, there are U-shaped, flat-based scars that are highly characteristic. Occasionally kidneys are seen at autopsy in which pyelonephritis has progressed so far that there are no individual scars, but the entire surface is contracted and shows a very characteristic appearance of extremely fine granularity of the surface.

In regard to size, the kidney in malignant nephrosclerosis is essentially normal. In chronic glomerulonephritis, the kidneys are usually very small; indeed, the smallest kidneys seen at autopsy are those seen in patients who have died of this disease. In pyelonephritis, the kidney is usually moderately reduced in size.

The kidney pelvis in malignant nephrosclerosis is relatively normal as far as size is concerned. A few petechiae may be seen. As the kidney contracts in chronic glomerulonephritis, it contracts in all directions, and the pelvis is dilated because of the loss of renal substance. In pyelonephritis the pelvis is dilated but it is likewise deformed because of variation in degree of involvement.

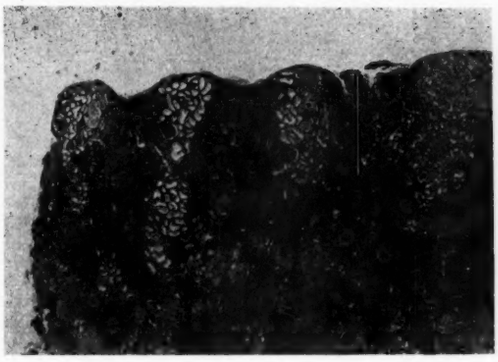

FIG. 1. A section of the cortex of the kidney showing tubular dilation and scarring with resultant nodularity of the surface. 20 X.

Dr. Owen will now describe the significant gross findings in this case.

DR. JAMES G. OWEN: The kidneys were much reduced in size, weighing 60 Gm. each. The cortical surfaces were pale and coarsely granular; they cut with a gritty resistance, revealing smooth, firm, pale parenchyma in which the cortico-medullary boundary was not well defined. The cortex was only 4 mm. thick; no petechiae were seen. The renal pelves were slightly dilated, but the ureters were normal

DR. MOORE: I think it is very evident that on the basis of gross examination, a diagnosis of chronic glomerulonephritis can be made.

DR. OWEN: The heart was greatly enlarged and weighed 690 Gm. The pericardium was thickened and adherent to the epicardium by tough, elastic, fibrinous adhesions which obliterated the pericardial cavity. The walls of the ventricles were thickened.

DR. MOORE: The other organs, so far as the gross examination was concerned, were normal. The diagnosis from a microscopic

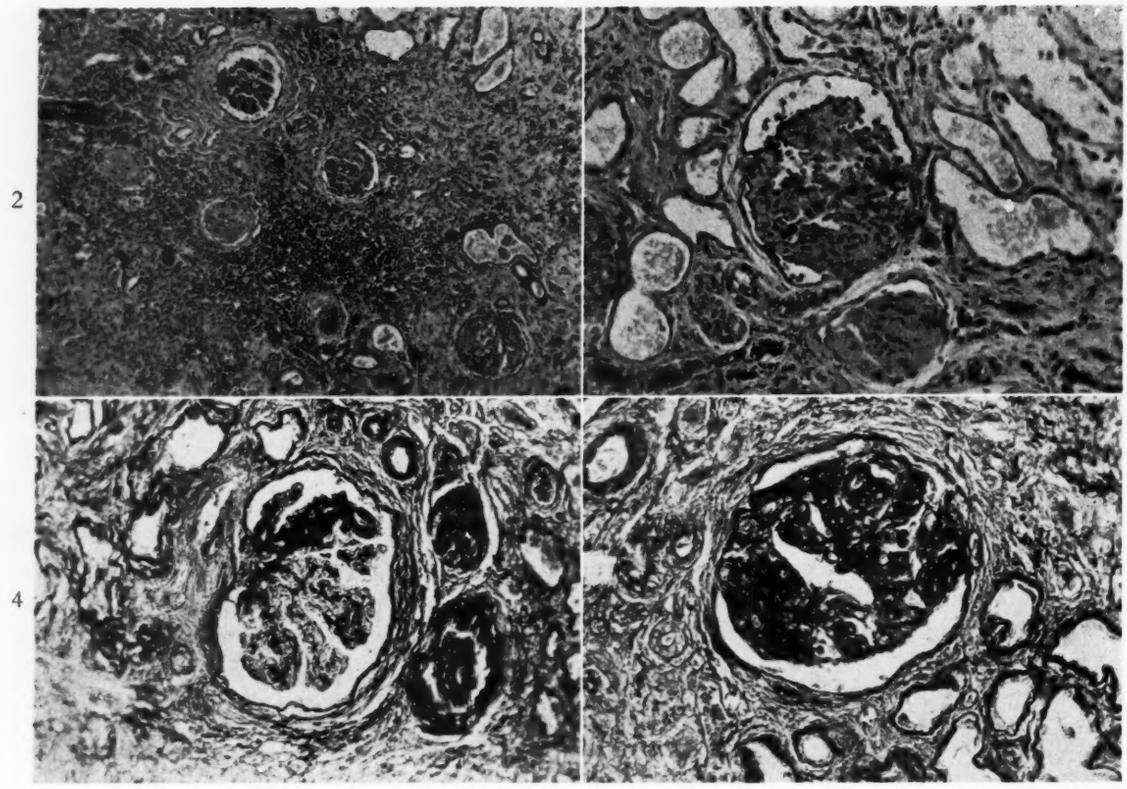

FIG. 2. Section of the renal cortex showing fibrosis, cellular infiltration and variations in the degree of glomerular involvement. 47 X.

FIG. 3. A section of the kidney showing a glomerulus with capsular adhesions and an increase in the number of nuclei. 100 X.

FIG. 4. Section of the kidney showing partial infarction of a glomerulus and thickening of the capsule; Heidenhain's stain. 100 X.

FIG. 5. Section of the kidney showing sclerosis of the capillaries in the glomerulus and capsular adhesions. 100 X.

standpoint was essentially the same as in the gross, though there are variations which will be discussed herewith.

The first section (Fig. 1) shows three nodules on the surface of the kidney. The tubules are greatly dilated and lined by epithelium of the type seen in the proximal convoluted tubules; the cells are not, however, quite so tall as normal. The depressions represent scar tissue. In this section the reason for the difference in the character of the nodularity in malignant nephrosclerosis and chronic glomerulonephritis may be seen. The former is a diffuse disease of the entire kidney and affects it uniformly; in an inflammatory process such as glomerulonephritis, the involvement varies in degree.

In Figure 2, a section of the cortex is seen. The photomicrograph shows at least six glomeruli; the pathologic change is not identical in any two. There is tremendous thickening of Bowman's capsule and an increase in the cellularity and a decrease in the lobulations of the glomeruli. One of the glomeruli is completely destroyed and replaced by fibrous tissue which is still moderately cellular. In another, glomerular adhesions are seen, and in a third, there is fibrosis of one part while the remaining part shows essentially normal structure. In general, it can be said that the more glomeruli involved, and the less uniform the involvement, the more likely the diagnosis of chronic glomerulonephritis. Therefore, from

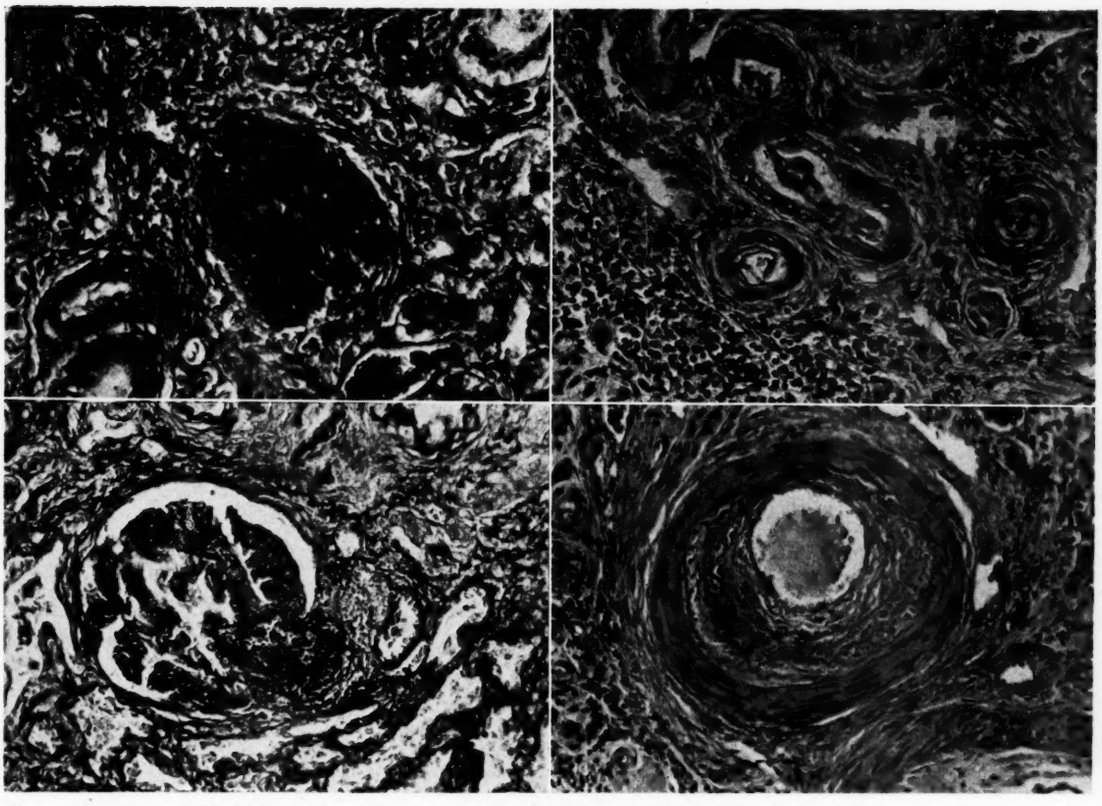

Fig. 6. Section of the kidney showing a totally obliterated glomerulus. 100 X.

Fig. 7. Section of the kidney showing several arterioles, with thickening, hyalinization of the walls and edema. 400 X.

Fig. 8. Section of the kidney showing necrosis of the afferent arteriole of a glomerulus and beginning infarction. 100 X.

Fig. 9. Section of the kidney showing a small artery in the cortex that exhibits thickening of the intima. 100 X.

this section of the cortex, the gross diagnosis of chronic glomerulonephritis may be supported. The rest of the cortex shows extensive fibrosis, destruction of tubules with flattening of the epithelium, and slight to moderate cellular infiltration with lymphocytes. The amount of cellular infiltration is not of too much value in differential diagnosis; it is extremely marked in pyelonephritis, least conspicuous in nephrosclerosis and varies considerably in glomerulonephritis.

In the next section (Fig. 3) the details of the glomerular change are shown. A typical glomerulus is seen; it shows capsular adhesions, alteration in the character of the cells lining Bowman's capsule, an increase in the number of nuclei within the glomerulus, and adhesions between the glomerular tufts. These changes are not seen to any extent in either of the other two types of chronic renal disease discussed. In Figure 4 Heidenhain's stain for connective tissue was used; a glomerulus is seen in which one area shows advanced change while other areas show no change at all. In the next section (Figure 5) the process is more marked; the glomerulus has become a single mass, the lobules have become adherent to one another, and thickening of the basement membrane is not seen to the degree common in arteriolar nephrosclerosis. In Figure 6, a totally obliterated glomerulus with a mass of fibrous tissue containing a few cells is seen. Under higher magnification nuclei were seen in

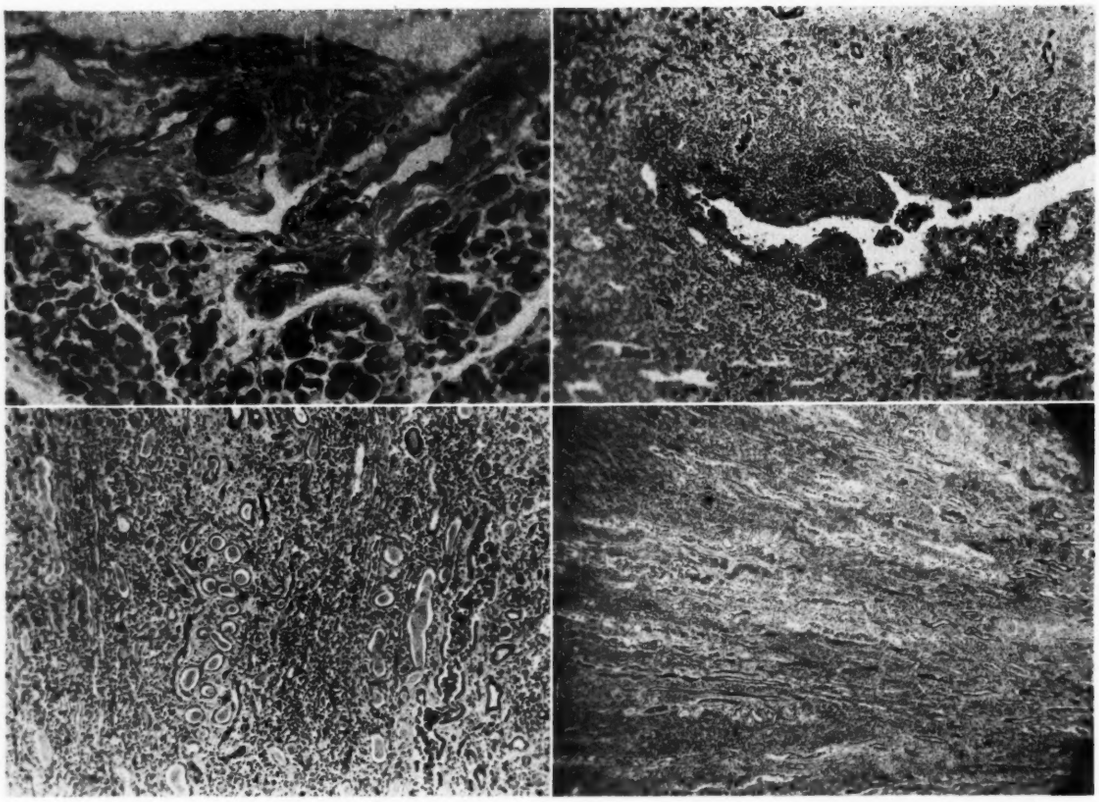

FIG. 10. Section of the pancreas showing several arterioles in the pancreas. They exhibit thickening and hyalinization of the walls as well as necrosis. 100 X.

FIG. 11. Section of the renal pelvis showing desquamation of the epithelium, lymphocytic infiltration and fibrosis. 20 X.

FIG. 12. Section of the kidney medulla showing cellular infiltration, fibrosis and hyaline casts in the tubules. 30 X.

FIG. 13. Section of the kidney medulla showing the characteristic pattern of cellular infiltration in pyelonephritis. 20 X.

the middle of the connective tissue; they would not be present if the changes were due to malignant nephrosclerosis.

In Figure 7 a group of arterioles in the kidney are seen; they are tremendously thickened and the walls are hyalinized in some areas. Each arteriole in the section shows these changes. In one of the vessels, it can be seen that the wall is edematous and occludes the lumen. This thickening of the arterioles is certainly an indication that the patient had arteriolar nephrosclerosis to at least some extent. The edema of the walls of some of the arterioles points to the possibility that the changes of malignant phase of nephrosclerosis might be found. The next section (Fig. 8) shows an entering arteriole of a glomerulus; the wall of the arteriole has undergone necrosis and there is a thrombus in the lumen and beginning infarction of the glomerulus. In Figure 9, a small artery in the kidney is seen; it gives evidence that there was also a certain degree of arterial nephrosclerosis which may have played a part in bringing about the marked decrease in the size of the kidney. The intima is greatly thickened, the lumen is perhaps one-third normal size, but the muscularis is fairly normal. In the next section (Fig. 10) a group of arterioles in the pancreas are

shown; again there is necrosis of the wall of these arterioles. The foregoing changes allow diagnosis of both chronic glomerulonephritis and malignant nephrosclerosis to be made.

Figure 11 is a section of the renal pelvis; there is desquamation of the epithelium. There is marked infiltration of the submucosa with lymphocytes and mononuclear cells; fibrosis is prominent. These changes are characteristic of pyelonephritis. Figure 12 is a section from the medulla showing fibrosis, cellular infiltration, and numerous hyaline casts in the tubules. These changes were not seen in the sections of the cortex, but were confined to the medulla and very largely to the region immediately surrounding the pelvis. In the next section (Fig. 13) the pattern of cellular infiltration within the medulla is seen. It extends in streams between the tubules. This change is also characteristic of chronic pyelonephritis but not of the other two diseases under discussion.

From the standpoint of pathologic anatomy this patient had chronic glomerulonephritis, malignant nephrosclerosis and chronic pyelonephritis; however, there is little doubt that the most widespread lesions are those of chronic glomerulonephritis. I do not think that pyelonephritis played an important part in the patient's clinical course; the most significant disease was the glomerulonephritis; to it was added, as is so frequently the case, arteriolar disease. During the terminal stage of the illness, the patient developed a slight degree of the malignant phase of arteriolar nephrosclerosis.

DR. ALEXANDER: In your opinion what was the duration of the chronic glomerulonephritis?

DR. MOORE: The findings are compatible with the clinical history of approximately fifteen months. However, the process may have been present for a number of years; it is difficult to be sure since the course of the disease is extremely variable.

Final Anatomical Diagnosis: Chronic glomerulonephritis; arteriolar nephrosclerosis, with necrosis of arterioles; chronic pyelonephritis; arteriolosclerosis, generalized; hypertrophy and dilatation of the heart (690 Gm.); ecchymoses and petechiae in the skin, lungs, pericardium, diaphragm, and mucosa of the stomach, colon and urinary bladder; organizing fibrinous pericarditis with obliteration of the pericardial cavity.

Editor's Note: After the conference, Dr. Willard Allen made the following suggestion, namely, that the "salt losing" phenomenon, by affording a mechanism whereby salt was lost and edema thus inhibited, may have explained the patient's apparently uneventful pregnancy.

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Case Reports

Carcinoma of the Prostate Gland*

Report of a Patient Treated with Orchiectomy and Estrogens

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DURING the past decade carcinoma of the prostate gland has been subject to biochemical and endocrinological lines of investigation yielding important results. In 1935, Kutscher and Wolbergs[1] described the occurrence in high concentration of an "acid" phosphatase in normal human prostatic tissue. The following year Gutman, Sproul and Gutman[2] demonstrated that metastatic prostatic carcinoma tissue in the bones had a high "acid" phosphatase content. Subsequently it was shown by the Gutmans[3,4,5] that the level of the serum "acid" phosphatase activity was specifically increased in patients with metastasizing carcinoma of the prostate.

In 1941, an advance in the management of prostatic carcinoma was made by Huggins[6,7] who described a fall in elevated serum "acid" phosphatase values and clinical improvement in patients with this disease following castration. This procedure was widely adopted, and early reports were universally hopeful. Patients who were followed over a period of a few months experienced cessation of bone pain and a gain in weight. Decrease in prostatic size, softening of hard prostatic nodules, *x*-ray evidence of regression of metastatic lesions and fall of the serum "acid" phosphatase levels to normal were noted.[8,9,10] When longer follow-ups became available, however, it was apparent that orchiectomy did not cure prostatic carcinoma, but was merely a palliative procedure, metastases recurring usually after a symptom-free period of six to twenty-four months.[11,12,13] For example, Nesbit and Cummings,[14] in 1942, reported on seventy-five cases followed for at least six months, of whom fifty-five had had good responses to orchiectomy. These authors described the same group of patients two years later[15] and indicated that twenty-one of the fifty-five apparently successful cases had had recurrences, and several had died. Similarly, Bumpus, Massey and Nation[16] reported immediate relief in most cases following orchiectomy but 49 per cent recurrences in one year.

Administration of estrogens alone was first recommended by Herbst,[17] and since has been advocated either as adequate therapy without orchiectomy or as adjunctive therapy to be given after orchiectomy, either routinely or when metastases reappear.[18,19,20]

The following case report describes a study of a patient with carcinoma of the prostate gland over a five-year period of hospitalization, and is presented because it offers an opportunity for correlation of the clinical course, *x*-ray findings and laboratory data.

CASE REPORT

D. G., a seventy year old Jewish man, was admitted to Goldwater Memorial Hospital on September 6, 1940, at the age of sixty-five, with a chief complaint of pain in the joints for two

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years. The patient had been well and pursuing his occupation as tailor until 1938 when, at the age of sixty-three, he began to have pains at first in his hips, and later in his knees, elbows, shoulders and wrists. In 1939, he was admitted to another hospital where a diagnosis of osteoarthritis was made and physiotherapy was prescribed. He was transferred to Goldwater Memorial Hospital for further care on September 6, 1940. His past health, except for a hemorrhoidectomy and a right cataract extraction had been good. The system review was negative except for some nocturia for the past year.

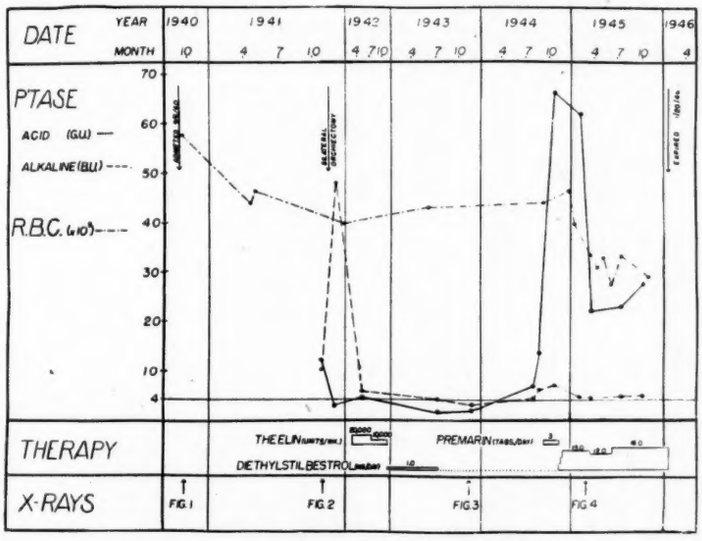

CHART. Course in the hospital.[11]

Physical examination on admission revealed the patient to be an elderly man whose chief findings consisted of flexion deformities of the knees, with swelling and limitation of motion of the knees, ankles, hips, elbows and wrists. The head revealed a right aphakia and a left cataract. The neck was not abnormal. The lungs were normal to percussion and auscultation. The heart was normal in size and showed regular rhythm and a rate of 80. The heart sounds were of poor quality and there was a soft apical systolic murmur. The blood pressure was 150 mm. of mercury systolic and 70 mm. diastolic. The abdomen showed no abnormality. The prostate was described as "firm, nodular, non-tender."

The complete blood count was normal, with red blood cells numbering 5.8 millions per cu. mm. and hemoglobin 90 per cent (Sahli). The erythrocyte sedimentation rate was 64 mm. in one hour (Westergren). The blood urea nitrogen was 16.0 mg. per cent and the fasting blood sugar 88 mg. per cent. The urine was acid with a specific gravity of 1.020, contained no detectable albumin or sugar and had a normal sediment. The blood Wassermann test was negative. Electrocardiography revealed only a left axis deviation. *X*-ray studies of the knees, hips, spine and hands revealed findings compatible with the diagnosis of rheumatoid arthritis and osteoarthritis. At this time there were no lesions in the bones which could be interpreted as those resembling metastases. (Fig. 1.)

The admission diagnoses were: (1) Rheumatoid arthritis and osteoarthritis; (2) benign prostatic hypertrophy.

In 1940, the patient was given salicylates for pain and whirlpool baths for his legs. He was confined to bed, but was afebrile and fairly comfortable.

In 1941, the treatment was continued as before, and during the first few months of the year he was gradually allowed up in a wheelchair. In September, however, he stated that for the past few months his peripheral joint pain had gradually grown worse. He also complained of pain in the spine, and it was most severe in the hips. His nocturia had continued, and now he also complained of frequency, burning on

urination and occasional dribbling. He had been feeling poorly and his appetite had decreased. Physical examination at this time revealed tenderness over the sternum, costal margins, spinal column and sacrum. Rectal examination revealed the prostate to be "enlarged to the size of a small apple, tender, stony-hard and coarsely nodular." His residual urine was found to be 100 cc. The blood urea nitrogen was 35 mg per cent. Examination of the urine revealed no abnormality. *X*-ray studies at this time revealed diffuse osteolytic and osteoplastic lesions throughout the pelvis and upper femora (Fig. 1), the dorsal and lumbar spine and the ribs. These findings strongly suggested generalized metastases. Phosphatase determinations at this time revealed values for "acid" phosphatase of 12.6 Gutman units and of 10.1 Bodansky units for "alkaline" phosphatase. A diagnosis of carcinoma of the prostate gland with widespread metastases was made.

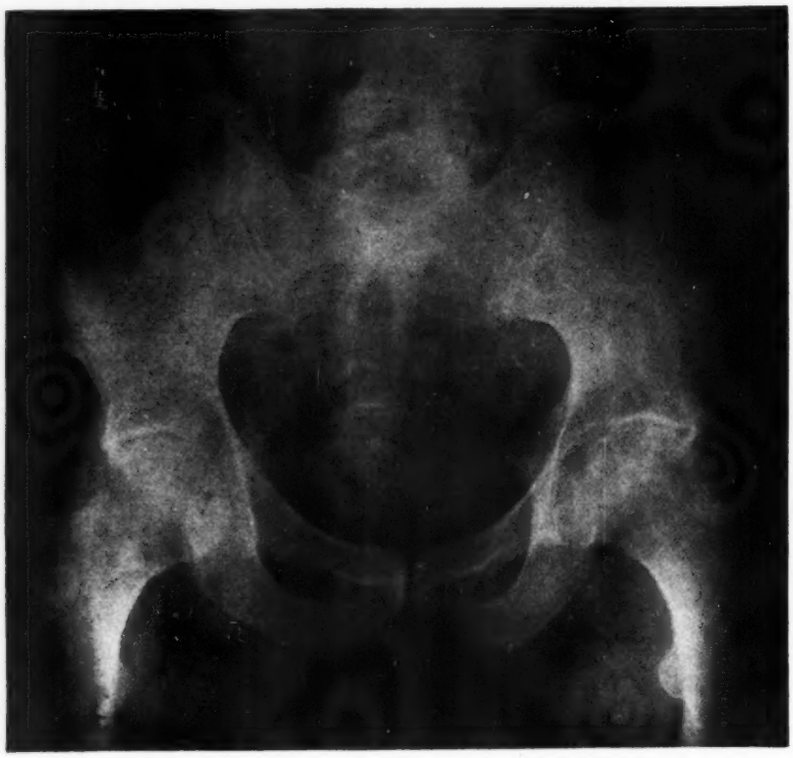

FIG. 1. September 26, 1940. The pelvis shows no evidence of metastases.

On November 13th, a bilateral orchiectomy was performed. Over the next month the patient's pain diminished markedly and he experienced an increase in appetite and in general had a greater sense of well being. The residual urine and dribbling disappeared and the frequency diminished. On November 28th, the "acid" phosphatase had fallen to 2.9 G.U. per cent and the "alkaline" had risen to 48.2 B.U. per cent. *X*-rays of the spine and pelvis at this time revealed no change from the previous films. The red blood cell counts during this year were around 4.5 million per cu. mm. with hemoglobin concentrations around 90 per cent. His further progress is indicated on the accompanying chart.

During 1942 the patient was free of pain (except for peripheral joint pain due to his arthritis) and was up in a wheel chair. In February, rectal examination revealed the prostate to be "about half the size it was before operation and much softer in consistency." At this time the findings on *x*-ray films of the bony pelvis were still unchanged. From March to July the patient received 10,000 U. of theelin by injection twice weekly and from July to December 10,000 U. were given once weekly.

In December, he was placed on 1 mg. of diethylstilbestrol a day by mouth. In May, the "acid" phosphatase was 4.3 G.U. per cent and the "alkaline" 5.9 B.U. per cent. *X*-ray studies in December showed bone regeneration in the pelvis and lumbar spine and no evidence of metastases in the ribs or dorsal spine.

During 1943 the patient's only complaints were referable to his peripheral joints and he required only salicylates for pain. Subjectively he was relatively well. The red blood count was 4.3 million per cu. mm. with a hemoglobin concentration of 85 per cent. The urine showed a trace of albumin and many leukocytes in the sediment, but was otherwise normal. The blood urea nitrogen was 21.6 and 17.6 mg. per cent on two determinations. The erythrocyte sedimentation rates were 51 and 71 mm. in one hour on two occasions. From January until July he received 1 mg. of diethylstilbestrol a day by mouth. In July, the "acid" phosphatase was 1.9 G.U. per cent and the "alkaline" 4.0 B.U. per cent and in December these values were 2.2 G.U. per cent and 3.0 B.U. per cent, respectively. In July, *x*-rays of the spine and pelvis showed considerable bone regeneration and in November (Fig. 3) there was disappearance of all the bone changes which had resulted from metastatic foci. Rectal examination, however, at this time revealed an "enlarged, hard prostate."

The patient continued well throughout 1944. In July, however, when the patient's only symptom was joint pain, the "acid" phosphatase was found to be 7.1 G.U. per cent and the "alkaline" 4.4 B.U. per cent. One month later these values were 13.7 G.U. per cent and 6.3 B.U. per cent, respectively. Rectal examination at this time revealed that the prostate was "normal sized, nodular, irregular, firm." *X*-rays of the pelvis revealed no evidence of metastases, but there was a small area of decalcification in the neck of the right femur which could be interpreted as a metastatic lesion. The patient was given a natural conjugated estrogen (Premarin). On October 17th, the "acid" phosphatase was found to be 66.3 G.U. per cent and the "alkaline" 7.2 B.U. per cent. There was a female pubic hair line, but no hypertrophy of the breast tissue, and it was decided

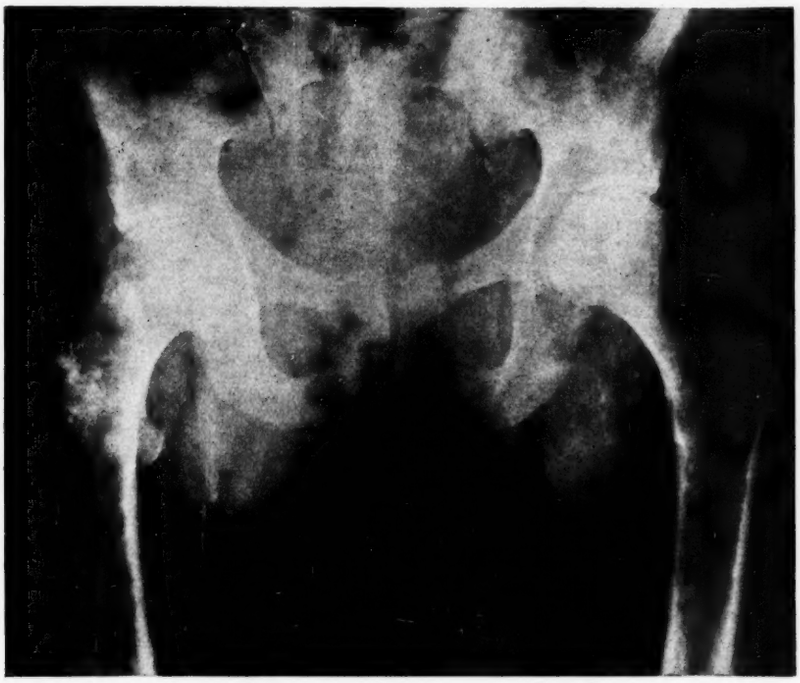

FIG. 2. October 23, 1941. There are diffuse osteolytic and osteoplastic lesions throughout the pelvis, upper femora and lumbar vertebrae. These findings are strongly suggestive of generalized metastases.

to give large doses of estrogenic substances. Accordingly, the patient was placed on diethylstilbestrol 5 mg. three times a day by mouth. Rectal examination revealed a "flat, firm, nodular prostate." His red blood cell counts during 1944 were around 4.4 million per cu. mm. and hemoglobin concentrations averaged 90 per cent. The urine continued to show a trace of albumin with many leukocytes and occasional erythrocytes in the sediment. The blood urea nitrogen was 18.3 mg. per cent, and the erythrocyte sedimentation rate was 68 mm. in one hour.

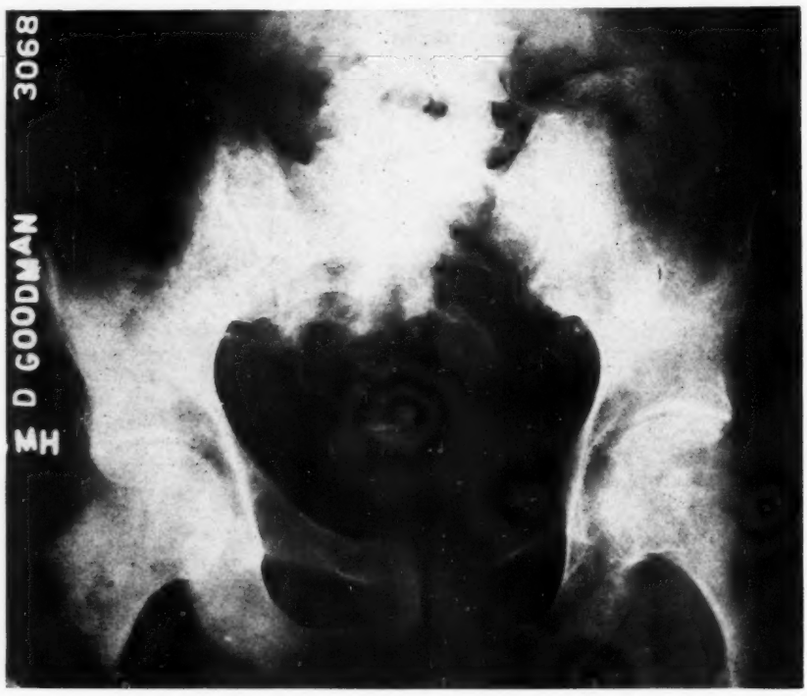

FIG. 3. November 17, 1943. The pelvis and upper ends of the femora show considerable bone regeneration. There are no metastases to the vertebrae.

The patient was subjectively well until the middle of 1945, when he began to experience progressive increase in pain in the back, pelvis and hips which required 60 mg. of codeine subcutaneously every six hours. He was unable to carry on wheelchair activity and he became progressively weaker and paler. His appetite began to fail. The red blood cell counts were in the range of 3.3 million per cu. mm. with hemoglobin concentrations of around 70 per cent. Twice the red count fell below 3.0 million to 2.9 and 2.7 million per cu. mm. The urinary findings were unchanged and the blood urea nitrogen was 13.9 and 17.7 mg. per cent on two occasions. The erythrocyte sedimentation rate was in the range of 73 to 102 mm. in one hour in six determinations. One Gm. of ferrous sulfate a day was given without appreciable effect. The "acid" phosphatase in January was 62.2 G.U. per cent and the "alkaline" 4.8 B.U. per cent. On 15 mg. of stilbestrol a day the patient had shown enlargement of the breasts with pigmentation and enlargement of the nipples and areolae. The female pubic hairline persisted. In February, *x*-rays of the spine and pelvis showed reappearance of osteoplastic metastatic lesions. (Fig. 4.) In March, because of gastrointestinal intolerance the dose of stilbestrol was temporarily decreased to 12 mg. a day. At this time the "acid" phosphatase was found to have fallen to 22.4 G.U. per cent with 4.4 B.U. per cent for the "alkaline" phosphatase. Because of this fall the dose of stilbestrol was increased to 16 mg. a day which was supplemented with 4 cc. of aluminum hydroxide gel and was tolerated by the patient. However, no change in the patient's downward course oc-

curred, and in July and October the "acid" phosphatase values were 23.3 and 27.7 G.U. per cent, respectively. The corresponding "alkaline" phosphatase values for these determinations were 4.9 and 5.0 B.U. per cent. Rectal examination in August showed a "slightly enlarged, fixed, irregular, firm prostate." In October, *x*-rays showed evidence of osteoplastic metastases in the ribs with a pathological fracture of the seventh rib on the right side.

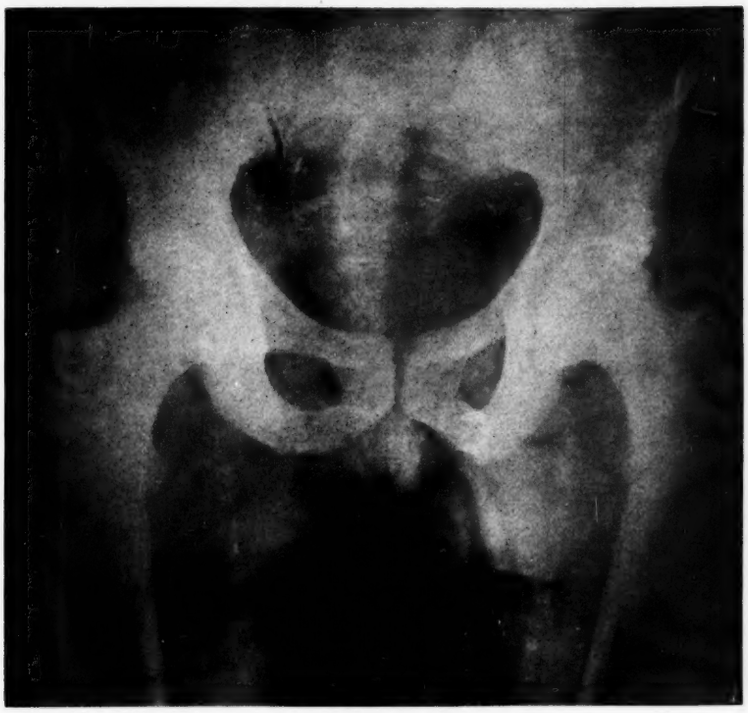

FIG. 4. February 28, 1945. The lumbar spine and pelvis show osteoplastic metastatic lesions.

In 1946 the patient was very feeble and markedly emaciated. He ate poorly and had continuous pain requiring 60 mg. of codeine every six hours. He expired on January 20th. In the postmortem handling of the body a fracture of the right humerus occurred.

The final clinical diagnoses were: (1) Carcinoma of the prostate gland with generalized metastases to the bones; (2) rheumatoid arthritis and osteoarthritis.

A postmortem examination was performed twenty-four hours after death. The body was that of a poorly nourished, poorly developed white male with marked evidence of recent weight loss. There was marked pallor of the entire body. There was a fracture of the right humerus (postmortem).

Gross examination showed that the head was not unusual. The brain was not removed. The breasts were prominent, and the areoli were deeply pigmented. Much fat and glandular tissue was noted in the breasts, and on cut section, a small amount of creamy white liquid exuded. The lungs were emphysematous and somewhat congested. The heart was small and weighed 200 Gm. The myocardium was dark brownish-black in color. The endocardium was slightly thickened, and the valves presented some slight calcific changes in the rings. The coronary arteries showed sclerosis, but were patent. The aorta presented numerous intimal ulcerations, with thrombus formation especially in the abdominal portion. The gastro-intestinal tract presented no abnormalities. The liver weighed 1,100 Gm. It was dark brown and on cut section presented a homogenous smooth surface, on which the lobulations were markedly increased. There were many small dark blue mottled areas. In the head of the pancreas there was a firm, granular fibrotic, grayish area. The rest of the

pancreas was normal. The spleen was small, pink-violet in color and firm. The left kidney was larger than the right and weighed 150 Gm. The architecture was normal. The right kidney was small, weighing 50 Gm. The surface was smooth. On cut section the cortex was almost completely absent, and there was poor demarcation of the medulla. The right renal artery was completely occluded at its origin by a well organized thrombus, which extended from an old thrombus of the aorta. The adrenals were normal in size and on cut section. The urinary bladder was small, contracted, and thickwalled, with numerous submucosal hemorrhages. An occasional small cystic area was noted in the mucosa. The prostate was small but very firm. The external surface was irregular. On cut section it presented a moderately firm, homogenous, grayish-white surface with numerous small yellowish-white, stony hard nodules. Section through several vertebrae showed a pale and friable marrow. The penis was normal. There were scars in the scrotum which represented the incision for the old bilateral orchiectomy. The extremities revealed only pallor of the nailbeds.

Microscopically, the left lower and right lower lobes of the lungs revealed dilated alveoli, anthracotic pigment and congestion. In the liver there was a marked deposition of hemosiderin both intra- and extracellularly. Small patchy areas of fatty degeneration and atrophy with fibrous tissue replacement were noted. Special stain showed hemosiderosis. There was much diffuse hyperplastic sclerosis of the Malpighian arteries of the spleen, with hemosiderosis. Sections through the pancreatic head showed marked hyalinization and fibrosis of the islet cells and acini, with fibrosis and tissue replacement. A large portion of tissue could not be evaluated because of postmortem tissue degeneration. The larger vessels showed varying degrees of sclerosis. One artery showed marked hyperplastic intimal thickening with almost complete obliteration of its lumen. The left kidney showed an increase in the number of the glomeruli but the architecture was otherwise normal. The small arteries showed mild thickening of the walls. The afferent arterioles also showed moderate thickening of the walls. The right kidney showed generalized atrophy, with hyalinization of the glomeruli, and interstitial fibrosis. Many hyaline casts were present in the collecting tubules. The larger arteries showed advanced arteriosclerosis with marked diminution of their lumina. Areas of old infarctions with fibrosis were seen. Localized collections of lymphocytes were seen in the interstitial tissue. Sections through the prostate showed the presence of large numbers of irregular acini, as well as individual collections of cells arranged in cords. These cells were irregular in outline and were hyperchromatic. They showed rapid proliferation and invasion into adjacent structures. The bladder mucosa was infiltrated with a considerable number of inflammatory cells, mostly lymphocytes and plasma cells. In areas the mucosa was seen to dip downward, forming gland-like spaces. Large, irregular, hyperchromatic prostatic cells were seen to invade the bladder wall. The breasts showed some hyperplasia of the glandular elements with some dilatation of the ducts. An amorphous pink staining material was noted in the ducts. Section through the bone showed the bony trabeculae to be partly broken up in areas, and the marrow, which was fibrous, was infiltrated by large masses of cells. These had an irregular acinar arrangement but frequently showed disruption of the basement membranes. The component cells had small dark nuclei which varied considerably in size and staining characteristics and had abundant eosinophilic cytoplasm. No osteoblastic increase was noted. The process consisted primarily of bone destruction rather than new bone formation.

The final pathological diagnoses were: (1) Adenocarcinoma of the prostate with metastases to bone and bladder wall; (2) hypertrophy of glandular elements of the breasts (due to estrogenic therapy); (3) absence of testes (previous operative removal); (4) chronic cystitis, and (5) atrophy of the right kidney due to arterial obstruction by an old thrombus.

COMMENT

This patient's course was similar to that of most patients with prostatic carcinoma who are diagnosed after metastases have

occurred and who are then subjected to orchiectomy. In this instance, however, the velocity of the disease seems to have been slower, the course lasting four years and three months from time of definite diagnosis until the time of death. Also, the symptom-free period following orchiectomy in this patient was over three years, which is a longer time than usually elapses.

Although the pain in this patient was frequently difficult to evaluate because of the coexistence of arthritis, it was apparent that he had had marked and prompt relief of his bone pain following orchiectomy. It was believed that during the years 1942, 1943, 1944 and the first half of 1945, what pain he experienced was in the peripheral joints and was due to arthritis and not metastases. His prostate became smaller following orchiectomy, and its consistency became somewhat softer. On admission this patient was thought to have benign prostatic hypertrophy. However, in view of the slow course of the malignancy it seems possible that the prostate even then was carcinomatous. The *x*-ray findings in this patient changed in the expected fashion in response to orchiectomy, but it took two full years for complete disappearance of the abnormalities due to metastases. It is interesting to note that the primary lesion remained small after orchiectomy even though extensive metastases to the bones had reappeared, and at autopsy the prostate gland was found to be small.

The typical changes to be expected in the phosphatase values following orchiectomy were described in detail by Sullivan and the Gutmans.[5] Our patient showed similar changes. An important point in our case is that the "acid" phosphatase was the first index to recurrence of widespread dissemination of the carcinoma, rising to 7.1, 13.7 and 66.3 G.U. per cent in July to October, 1944. Subjective symptoms did not appear, however, until the middle of 1945. Also *x*-rays taken at the time of the rise in "acid" phosphatase showed only one area of decalcification which could be metastatic, and it was not until a few months later that generalized metastases appeared in the *x*-ray films.

Estrogens were used in this case first in small doses as routine postoperative therapy. In 1943, when the patient had shown restitution of bony architecture to normal, and the clinical course was satisfactory, estrogenic therapy was discontinued. Later, when the "acid" phosphatase began to rise, large doses of diethylstilbestrol were given. It may be noted that while on these doses our patient had a fall in "acid" phosphatase from 62.2 to 22.4 G.U. per cent. However, the clinical course was unaffected, and the drop in phosphatase may possibly have represented cellular and biochemical changes in the metastatic tissue rendering it less able to elaborate "acid" phosphatase as the patient approached a terminal state. The microscopic changes in breast tissue due to diethylstilbestrol have been described[21] and the changes found in our patient were similar.

The reason for exacerbation of prostatic carcinoma after clinical remission due to orchiectomy is not clear. Increased androgenic activity of the adrenal cortex has been postulated. Herbst[22] reported a series of cases in which the patients were treated with estrogens, of whom four had post-mortem examination of the adrenals. Of these, one showed hypertrophied adrenals. In a report of a case, Gilbert and Margoles[23] found the adrenals to be normal. In our patient the adrenals appeared grossly normal, but unfortunately no histological sections were available.

SUMMARY

1. A case of carcinoma of the porstate gland with metastases to the bones is presented because of the opportunity to study

over a prolonged period of time the correlation of clinical course, laboratory findings and *x*-ray with orchiectomy and administration of estrogens.

2. Orchiectomy was an effective palliative procedure. Following it, there was cessation of bone pain, improvement in appetite and increased sense of well being. The prostate became smaller and softer, bone metastases disappeared and elevated serum "acid" phosphatase values became normal.

3. Symptoms and *x*-ray and chemical signs of widespread metastases reappeared, however, after a period of more than three years.

4. Diethylstilbestrol was administered in large doses after signs of recurrence of metastases appeared. While receiving this drug, the patient was comfortable for several months before he began a final downhill course.

5. The serum "acid" phosphatase determination was an accurate and sensitive index to the existence of metastases from prostatic carcinoma.

We wish to express our gratitude to Dr. Henry K. Taylor who read and interpreted the *x*-ray findings.

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Renal Damage Resulting from Idiosyncrasy to Neoarsphenamine*

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SEVERE renal damage is a relatively rare complication of arsenical therapy. Stokes,[1] in regard to renal injury, states "This complication of the use of the arsenicals may be asserted to occur, for all practical purposes, only as the result of the administration of toxic doses or preparations." Likewise, Moore[2] states "There is, so far as we know, no adequate evidence that . . . the arsenical preparations . . . , given in average therapeutic dosage, will cause renal damage even in an already diseased kidney, except in association with other evidences of grave drug intoxication such as dermatitis, blood dyscrasias, severe stomatitis or enteritis." "All these renal reactions are fortunately very rare. In actual practice renal damage from the arsphenamines need not be feared." Acid arsphenamine has been found repeatedly to cause a severe hemorrhagic nephritis, but alkalinized arsphenamine rarely produces severe kidney damage.

Two patients with death resulting from renal damage due to mapharsen were reported during a six-year period, 1935 to 1942.[3] Another fatality from nephritis, which was attributed to mapharsen, was reported in 1944.[4] In an analysis of the results of triweekly mapharsen therapy, Eagle[5] found only four instances of severe renal damage occurring in 4,823 patients with the condition. Severe kidney injury as a result of arsphenamine is very rare.[6] Neoarsphenamine has been found to cause renal damage.[7] During a seventeen-year period, 1,355,058 doses of neoarsphenamine were administered in the Navy, with two fatal and five other severe renal reactions.[8] Four of these cases clinically simulated acute glomerulonephritis, with hematuria, albuminuria, anuria, azotemia and hypertension. In the others no hematuria or hypertension were present but instead a picture of acute nephrosis developed.

Experimental injections of massive doses of arsphenamine and neoarsphenamine in rats have been found to cause severe nephritis and usually death.[9] Therapeutic dosages, however, result in only very slight renal impairment. A few casts and a trace of albumin are not uncommon on the day following an arsenical injection, and the blood urea nitrogen value may be slightly increased. Elliott and Todd[10] studied renal function by measuring phenolsulfonphthalein excretion and the blood urea nitrogen level in a group of patients before and after arsphenamine injections. A slight reduction in renal function was noted in some cases after therapy. McFarland,[11] in a study of the effects of antiluetic therapy on the normal and diseased kidneys, found that arsphenamine causes only slight renal irritation and that neoarsphenamine appears to cause less reaction than arsphenamine.

Because of the rarity of renal damage as a result of neoarsphenamine therapy, and because recovery occurred following such an unusually severe reaction, it is thought worth while to report in some detail the following case history.

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CASE REPORT

M. N., a white female thirty-nine years of age, who had been known to have syphilis for eleven years, was found to have character changes and lapses of memory in 1944. She also complained of "lightning pains" in her legs at that time. In the summer of 1944, she received a course of malarial fever therapy, followed by ten mapharsen injections at weekly intervals. This was, in turn, followed by eleven bismuth injections during the winter of 1944 and 1945. During the course of malarial treatment in 1944, several blood urea nitrogen determinations were made as well as a number of routine urine examinations, all of which were normal. She complained of no urinary symptoms, such as burning or frequency. A phenolsulfonphthalein test in June, 1944, revealed 25 per cent excretion of the dye in thirty minutes and a total of 50 per cent excretion in sixty minutes.

On February 13, 1945, the patient received 0.1 Gm. neoarsphenamine intravenously without any untoward effect. This was, as far as can be determined, her first treatment with this drug. Subsequently, the patient did not return to the clinic for about six months.

In October, 1945, the patient began again to have frequent "lightning pains" in her legs. On October 18th, she received 0.2 Gm. neoarsphenamine intravenously. Within a few hours nausea and vomiting appeared. After six hours a purpuric rash appeared over her face and neck. A tourniquet test (Rumpel-Leede) the following day was normal. Intractable vomiting, loss of strength, weight loss, hematemesis and epistaxes developed and continued until the time of her hospital admission on October 26, 1945. The skin rash disappeared after three or four days, but at the time of admission, eight days after the injection of neoarsphenamine, she had the additional complaints of diarrhea and constant hiccoughing.

The patients' blood pressure on admission was 115/80, the pulse was 80, the temperature was 98.0°F. and the respirations were 22 per minute. The patient showed evidences of recent vomiting. Singultus was present. She was somewhat confused and her speech was thick and slurred. Her skin was very dry and there was evidence of marked loss of weight. There was pallor of the skin but no evidence of jaundice or rash was found. The tourniquet test (Rumpel-Leede) for capillary fragility again showed a negative reaction. A few small submaxillary, axillary and inguinal nodes were felt. The pupils reacted to accommodation but not light. Extra-ocular movements were normal. The fundi were normal. The nose and mouth were coated with dried, clotted blood. Examination of the heart and lungs revealed normal findings. There were no palpable abdominal masses. Some generalized abdominal tenderness was noted. Examination of the pelvic organs and rectum was negative. Neurologic examination revealed a coarse tremor of the outstretched hands, generalized weakness and diminished vibratory, position and pain sensation in the lower extremities. The patellar and achilles reflexes were absent, and no Babinski sign could be elicited.

The hemoglobin was 8.0 Gm. per cent. The volume of packed red blood cells was 30 cc. per cent. The icteric index was 4. Platelets were 400,000 per c.mm. (Rees-Ecker method). The white blood count was 8,400 per c.mm., with 7 per cent juveniles, 71 per cent neutrophils, 1 per cent eosinophils, 20 per cent lymphocytes and 1 per cent monocytes. The blood Kahn reaction was reported as doubtful. The spinal fluid which contained 5 lymphocytes per c.mm. showed a positive Kahn reaction and a colloidal gold curve which was 555555554. Urine examination revealed albumin (two plus) and two white blood cells per high power field in the centrifuged specimen. The urine was scanty, only 4 cc. being obtained in eight hours. The blood urea nitrogen level was 193 mg. per cent. Additional blood chemical data are presented in the accompanying table. Stool examination revealed no gross blood, and no pathogens were found in a culture of the stool. A phenolsulfonphthalein excretion test revealed no trace of dye after two hours.

Treatment at the hospital consisted of parenteral administration of large quantities of 5 and 10 per cent glucose solutions and plasma. The patient developed a diffuse, soft edema and her pallor became more pronounced. Nausea and vomiting continued unabated for seven

LABORATORY DATA

Date	Cc. Per cent Hemato-crit	W.B.C.	B'ood Urea Nitrogen Mg. Per Cent	Vol. Per Cent CO_2 Combining Power	Albumin Gm. Per Cent	Globulin Gm. Per Cent	Chloride Mg. Per Cent	Calcium Mg. Per Cent	Phos-phorus Mg. Per Cent
10/26/45	31	8,400							
10/29/45	27.5	15,700	193		3.2	1.6			
10/31/45			200	25					
11/1/45				22			610	9.9	8.2
11/5/45	25.5	9,000	212	28					
11/7/45	24.0	9,700							
11/9/45			156		4.6	1.7			
11/13/45			92				610		
11/15/45	22.0	5,700	63	44					
11/20/45			41	44	4.6	1.5			5.5
11/24/45	23.0	5,100							
11/26/45			41						
12/7/45			33	23					
1/4/46			16.5						

days and then ceased abruptly. At that time the blood urea nitrogen was over 200 mg. per cent and the phenolsulfonphthalein test again revealed no excretion. Oliguria of from 600 to 800 cc. of urine per day persisted for a week, after which time the urine volume increased rather suddenly. On November 3rd (nine days after admission), the patient was able to eat and drink without vomiting. She then began to show gradual improvement. The pulse rate remained normal and she was afebrile throughout her hospital stay. The blood pressure remained within normal limits. On November 9th, the blood urea nitrogen was 156 mg. per cent, on November 13th, 92 mg. per cent and on November 20th, 41 mg. per cent. The carbon dioxide combining power gradually rose from 22 volumes per cent on November 1st to 44 volumes per cent on November 20th. The serum albumin rose from 3.2 Gm. per cent on October 29th to 4.6 Gm. per cent on November 10th. However, the volume of packed red blood cells gradually declined until on November 24th, it was 23 cc. per cent. At that time she had a hypochromic, microcytic type of anemia.

Marked albuminuria was present for six days following admission. The albumin content then diminished, so that after the eighteenth hospital day no further albuminuria was noticed. Leukocytes were numerous in most samples of urine during her hospital stay but only rare erythrocytes or casts were seen. A urine culture was positive for Escherichia coli on November 16th, having previously been negative. Methenamine therapy was instituted and continued until discharge. At this time, thirty-two days following admission, the urine was normal. Phenolsulfonphthalein excretion was 10 per cent in fifteen minutes, 18 per cent total in thirty minutes and 25 per cent total in sixty minutes. The maximum concentration of the urine was 1.018 (specific gravity).

On December 7, 1945, seven days after discharge, the patient complained of slight weakness but was improving generally. The blood urea nitrogen now was 33 mg. per cent and the carbon dioxide combining power was 23 volumes per cent. The urine showed two plus albumin, 3 to 5 hyaline casts, 3 to 5 leukocytes and no erythrocytes per high power field of centrifuged urine.

On January 4, 1946, one month later, the patient had no complaints. The blood pressure was 110/80. The blood urea nitrogen was 16.5 mg. per cent. The urine showed a trace of albumin, a specific gravity of 1.015, no casts, no erythrocytes and ten leukocytes per high power field, after centrifugation.

On June 6, 1946, the patient was found to be feeling very well, was working and had no specific complaints. She was given an injection of 0.1 Gm. of bismarsen, which was followed by

nausea, vomiting, hematemesis and diarrhea for one week. However, there were no symptoms of urinary tract involvement during this episode.

The patient was last seen on June 26, 1946. At this time she had no complaints. She had no urinary tract symptoms of any kind. The urine at this time showed no albumin, no erythrocytes, no casts, and 3 to 5 leukocytes per high power field of the centrifuged specimen. The phenolsulfonphthalein test revealed 35 per cent excretion of the dye in thirty minutes and 50 per cent total in fifty minutes. Urine culture revealed Escherichia coli to be present. The total renal plasma flow, as measured by the paraminohippurate method,[12] was 225 cc. per minute per 1.73 sq. meters (Normal range: 491 to 695). Glomerular filtration according to the mannitol clearance test,[13] was 55.9 cc. per minute per 1.73 sq. meters (Normal range: 101 to 133).[14] Thus, the renal function was impaired to a moderate extent seven months after the acute episode.

COMMENTS

Because of an idiosyncrasy to neoarsphenamine the subject of this report appears to have developed purpura, a severe gastrointestinal reaction and severe renal damage which seemed to be primarily tubular in character. Through a previous injection of this drug, the patient probably developed sensitivity, which became manifest after the second injection eight months later. The amount of neoarsphenamine given was small enough to exclude direct toxic injury of kidney parenchyma.

Sensitivity reactions to neoarsphenamine and to other trivalent arsenicals are not uncommon, but the sensitivity is usually manifested only by the development of a skin eruption. Renal sensitivity reactions may be either mild or severe. There may be slight albuminuria, cylinduria and hematuria which disappear after a few hours or days. The picture of acute glomerulonephritis with anuria, hematuria, albuminuria, azotemia and hypertension may be seen or, as in this case, a picture of nephrosis may be encountered. Chemical nephrosis, due to bichloride of mercury, is characterized by degeneration and necrosis of the cells lining the convoluted tubules. Similar lesions have been described as a result of sensitivity to sulfonamides.[15] In the latter instances small doses of sulfonamides have produced the nephrotic syndrome and crystalluria has been absent in such cases. Anatomically, these lesions have been found to consist of thrombi in the interlobar arterioles and veins accompanied by evidence of tubular degeneration. The clinical picture in such cases is similar to that of chemical nephrosis in which azotemia, edema, oliguria, albuminuria and hyposthenuria are found while hypertension does not occur. In the present case, however, glomerular residual damage is indicated by the impaired mannitol clearance.

Because of the gastrointestinal symptoms which developed following a bismarsen injection six months after the severe neoarsphenamine reaction, it appears likely that the patient described here is hypersensitive to all trivalent arsenicals. Sensitivity to one arsenical denotes probable sensitivity to other arsenical preparations in most instances.[6]

SUMMARY

1. A review of the available literature reveals the relative infrequency of severe renal reactions following arsenical therapy.

2. A case is presented of severe nephrosis accompanied by purpura and gastrointestinal reaction which followed the administration of a small dose of neoarsphenamine.

3. Despite the severity of the reaction nearly complete recovery has occurred in this case.

4. The renal injury in this instance is thought to have been due to a sensitivity reaction. Clinically, the manifestations were similar to those of nephrosis caused by

bichloride of mercury and accompanying sulfonamide sensitivity.

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Aberrant Atrioventricular Conduction in a Patient with Paroxysmal Tachycardia, a Short P-R Interval and a Normal QRS Complex

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THE interesting physiologic aspects concerned with the condition known as aberrant atrioventricular conduction or Wolff-Parkinson-White syndrome[7] has recently led to increasing investigation and reporting of the subject. To explain the observed phenomena, Holzman and Scherf,[2] and almost simultaneously Wolferth and Wood,[6] postulated the existence of an accessory muscle bundle capable of bypassing the normal A-V conduction system and directing the impulse to one ventricle prematurely. Subsequently Wood, Wolferth and Geckler[8] actually demonstrated such a structure in an individual who during life exhibited evidence of Wolff-Parkinson-White syndrome with paroxysms of tachycardia. More recently Rosenbaum et al.,[5] in an exhaustive analysis of the problem stated, among other conclusions, that more than one accessory bundle may be present although not all may be functioning at the same time. It is believed that the impulse reaches the ventricles both by way of the accessory structure and the normal auriculoventricular system.

There is little diversity of opinion at present regarding the diagnostic criteria for this condition. These are summarized as follows: (1.) Shortened P-R interval, usually to .10 seconds or less; (2.) widened QRS complex, often .14–.16 seconds. The P-S interval (beginning of P to end of QRS) remains within the normal range; (3.) slurred initial stroke of the QRS complex. Additionally, there are often extensive degrees of axis deviation, commonly to the left, and individuals with this syndrome are subject to paroxysms of tachycardia. These are ordinarily supraventricular in origin but paroxysmal ventricular tachycardia has also been observed.[3] Auricular tachycardia is thought to occur when an impulse proceeds normally through the A-V node, the bundle of His and its branches but continues to complete a circus by returning to the auricle through the anomalous conductor.

There is some evidence, however, that one of the criteria, namely, abnormal widening of the QRS complex, may not be strictly valid. When the QRS complex normally is very brief, .04–.06 seconds, considerable widening may occur and still leave the total within the normal range. However, in such cases the initial portion of the ventricular complex shows characteristic slurring and the P-R interval is shortened. Fox[1] reported one such case in which the QRS was .08 seconds in duration. He was able to shorten it further by the administration of quinidine and to lengthen it with digitalis and prostigmine. He suggested that only two requirements are needed for the diagnosis of aberrant atrioventricular conduction, namely, a shortened P-R interval and a distorted QRS which may be of normal or lengthened duration.

Recently a case was observed which

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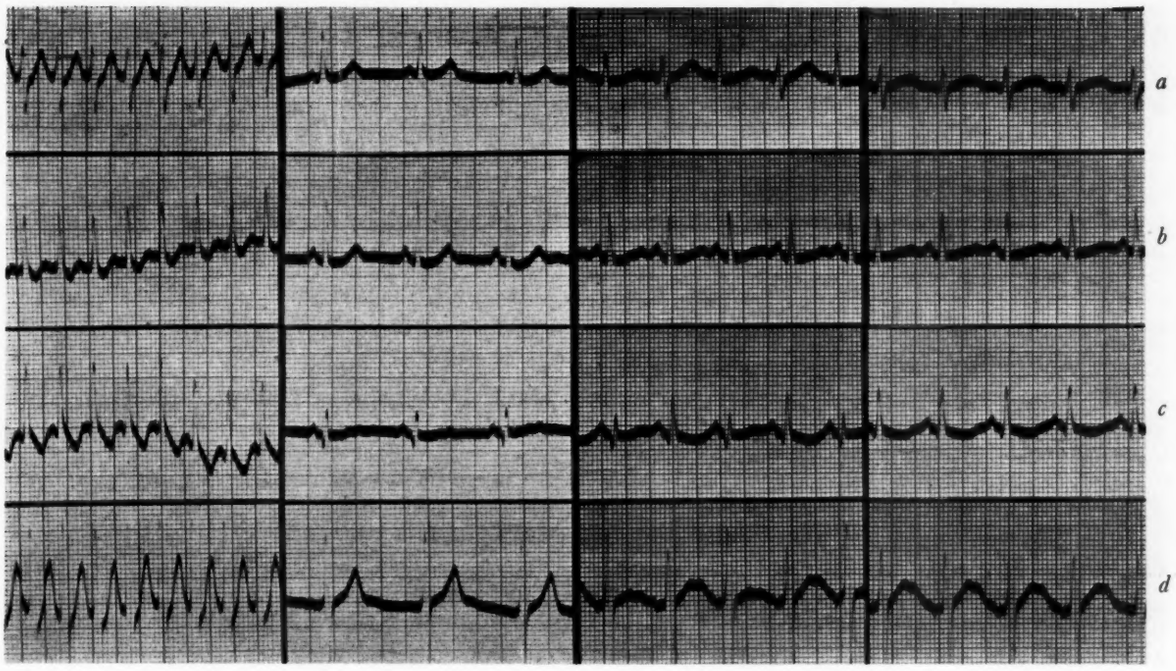

FIG. 1. *a*, Paroxysmal supraventricular tachycardia; *b*, "normal" pattern; *c*, following administration of quinidine; *d*, following administration of quinidine and atropine.

although fulfilling some of the requirements of accessory auriculoventricular conduction is not covered by even these modified criteria.

CASE REPORT

An opera singer, thirty-two years of age was admitted for study of attacks of rapid heart action. These had been present for seven years and were moderately disabling. The onset was sudden and unpredictable and the duration varied between a few seconds and several hours. The termination of the attacks was also abrupt and could sometimes be induced by ocular pressure. There were no other cardiac symptoms and the history was not otherwise significant. The physical examination was essentially normal. The heart was not enlarged, the rate was 68 and the rhythm was regular. No murmurs or thrills were noted. *X*-ray and laboratory studies were all within the normal range.

The electrocardiogram was remarkable only in that the P-R interval was .10 seconds in duration and the QRS .08 seconds. The axis was +34°, a small Q_3 was noted and the ventricular complex was otherwise undistorted and normal in appearance. It was thought to represent an instance of nodal rhythm. Following rather vigorous physical effort an attack of tachycardia was noted and recorded. The tachycardia was apparently auricular in origin, the rate was 210 per minute and a marked change in the appearance of the ventricular component was apparent. The axis had rotated 60° to +94°.

In view of the change in axis noted during the tachycardia and the previously observed short P-R interval the possibility of aberrant A-V conduction was considered. Attempts were made to widen the QRS complex with cholinergic drugs but these were not successful. At this point quinidine was employed in an effort to depress the aberrant conduction pathway and so demonstrate its presence. After preliminary administration of the drug to determine sensitivity the patient was given .6 Gm. of quinidine at intervals of one hour until three doses had been administered. Following the last dose a tracing was made which demonstrated an alternating shift of the axis without change in the P-R:QRS relationship. Every other beat strongly resembled the complexes observed during the paroxysm of tachycardia while the remainder were unchanged except for the overall effects of the drug. The patient was then given 1.0 mg. of atropine intravenously following which the electrocardiogram revealed complete reversion to the form

first noted during the tachycardia. However, the P-R interval remained unchanged to ordinary measurement and the QRS duration was unaltered.

COMMENT

Since all of the criteria were not fulfilled and most were merely indicated, this case could hardly be considered a characteristic example of Wolff-Parkinson-White syndrome. On the one hand, features were present which strongly suggested the influence of some type of accessory A-V conduction. The short P-R interval with attacks of paroxysmal tachycardia point to such a mechanism while the varying appearance of the QRS complex is consistant with altered ventricular distribution of the impulse. Further, the depressant action of quinidine on the postulated anomalous conductor was manifest through electrocardiographic changes which were further exaggerated by the use of atropine. On the other hand, the QRS complex was neither prolonged nor significantly deformed and no alteration in the P-R:QRS relationship occurred when the anomalous conductor was depressed and apparently inoperative during the administration of quinidine and atropine.

One would suspect, therefore, that if accessory A-V conduction was responsible for the observed phenomena in this subject, that a more complicated mechanism was at work. A number of reported instances of Wolff-Parkinson-White syndrome indicate the presence of several aberrant conductors apparently acting alternately or in various combinations. Cases No. seven and nine of this author's reported series[4] demonstrated striking changes in the form of the ventricular complex occurring spontaneously or following changes in position. This was thought to result from the varying action of several anomalous pathways. Wood, Wolferth and Geckler[8] in their pathologic description of accessory conduction demonstrated multiple anomalous channels. It is suggested, therefore, that in the patient under discussion, more than one accessory conductor was present and that they were unequally affected by the drugs employed and during the observed paroxysm of tachycardia.

Although it is apparent that no ready or simple explanation is available for the observed phenomena, it is believed that the subject represents one variant of accessory auriculoventricular conduction. It is, perhaps, remotely related to the syndrome of Wolff, Parkinson and White and may, in an even more attenuated form, be responsible for otherwise unexplained instances of paroxysmal tachycardia in apparently normal individuals.

SUMMARY

A case of anomalous atrioventricular conduction is described which does not conform to the usual criteria.

A mechanism is suggested to explain the observed phenomena.

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Editorial

The Question of "Spasm" of the Coronary Arteries

PHYSICIANS often postulate "spasm" of the coronary arteries to explain episodes of angina pectoris and other types of cardiac pain. Spasm could result from a direct effect of adrenalin or other chemical circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor impulses. Conclusive evidence for such coronary vasoconstriction is, however, fragmentary and incomplete. A vast literature of laboratory observations has been accumulated, but the results of experimental observation on various animals cannot be transposed to man with assurance; it is well known that even the reverse of phenomena observed in animals may be encountered in man. The rich supply of autonomic fibers to the coronary arteries implies a probable vasomotor function. Nevertheless, Gregg was led to conclude in a recent review[1] that "it would seem most difficult to establish and identify conclusively by experimental means the separate effects of nervous influences upon the myocardium and coronary vessels because the physiological functions of these structures are so intimately related that their individual responses may be secondarily modified, each by the other. . . . Until better instruments and methods are devised and used in conjunction with preparations which are capable of normal physiological responses, our knowledge concerning the normal and abnormal functioning of the coronary circulation will be necessarily limited as well as unavoidably inexact."

Studies in man obviate some of these uncertainties and afford important information. The fact that attacks may be brought on by exposure to cold or "by any disturbance of mind"[2] is difficult to explain solely on the basis of long standing intrinsic arteriosclerotic changes in the coronary arteries. Some episodes, particularly those occurring in the absence of effort or increased cardiac work, are best understood as the expression of vasoconstriction or absence of vasodilatation leading to a relatively insufficient coronary blood flow. Relatively recent observations in patients with angina pectoris afford strong evidence of the existence and significance of vasomotor influences. Gilbert, Fenn and Leroy[3,4] observed that patients while breathing 10 per cent oxygen developed pain much more frequently following meals. The increased susceptibility to angina pectoris following meals was abolished by the use of atropine. This evidence, while not conclusive because of possible lessened abdominal distention and other reactions after atropine, is, however, paralleled by other observations. Thus, Freedberg, Spiegl

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and Riseman[5] in a study of patients with angina pectoris found that holding an ice cube in one hand markedly reduced the capacity of their subjects to perform exercise without pain. This reaction to localized cold was evidently reflex in nature. Conversely, immersion of the hands and wrists in hot water increased the patients' ability to undertake exercise before developing pain. Various factors such as chilling or warming of the blood, changes in minute volume cardiac output, alterations in blood pressure or cardiac rate were excluded as causative influences.

Other clinical observations are of interest in this connection. In several subjects with angina pectoris, Wilson and Johnston[6] observed pronounced electrocardiographic changes of the type produced by temporary occlusion of a large coronary artery which appeared, disappeared and reappeared without any material increase in heart rate or in blood pressure. The character of the electrocardiographic changes suggested that the change in arterial or arteriolar caliber was local and not general. In two of their patients the typical anginal paroxysms were induced by smoking cigarettes. Whether the coronary arteries were affected by vasomotor influences or were directly affected by nicotine or some other constituent of cigarette smoke cannot be stated, although it is of interest to note that cigarette smoking produces constriction of the peripheral arterioles both in healthy subjects and in patients with angina pectoris. The amelioration of angina pectoris occasionally witnessed after gallbladder surgery with reversion of electrocardiographic changes toward normal likewise may represent interruption of vasomotor influences.[7]

The existence of vasomotor effects on the coronary circulation in no way invalidates the accepted recognition of the widespread pathological changes of arterial narrowing and occlusion in the hearts of patients with angina pectoris; on the contrary, this evidence supplements our understanding of the nature of cardiac pain and the mechanisms whereby it may be induced. The widespread pathologic lesions in the coronary arteries in patients with cardiac pain afford an adequate basis for the operation of the ischemic theory of pain. They must not, however, be considered the exclusive cause of cardiac pain, but rather as constituting the stage on which various factors may operate. Thus, vasoconstriction or absence of vasodilatation, anemia, tachycardia or the lowered blood pressure of shock may act as precipitating agents in the production of pain in a heart whose circulation is already compromised by arterial obstruction.

H. L. Blumgart, M.D.

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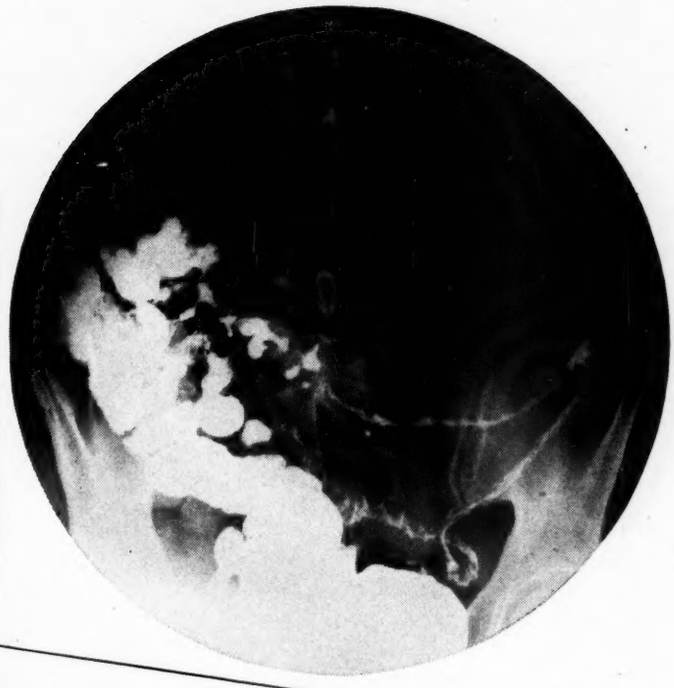

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†Fox, N. et al.: Arch. Otolaryng., *41*:279, 1945.

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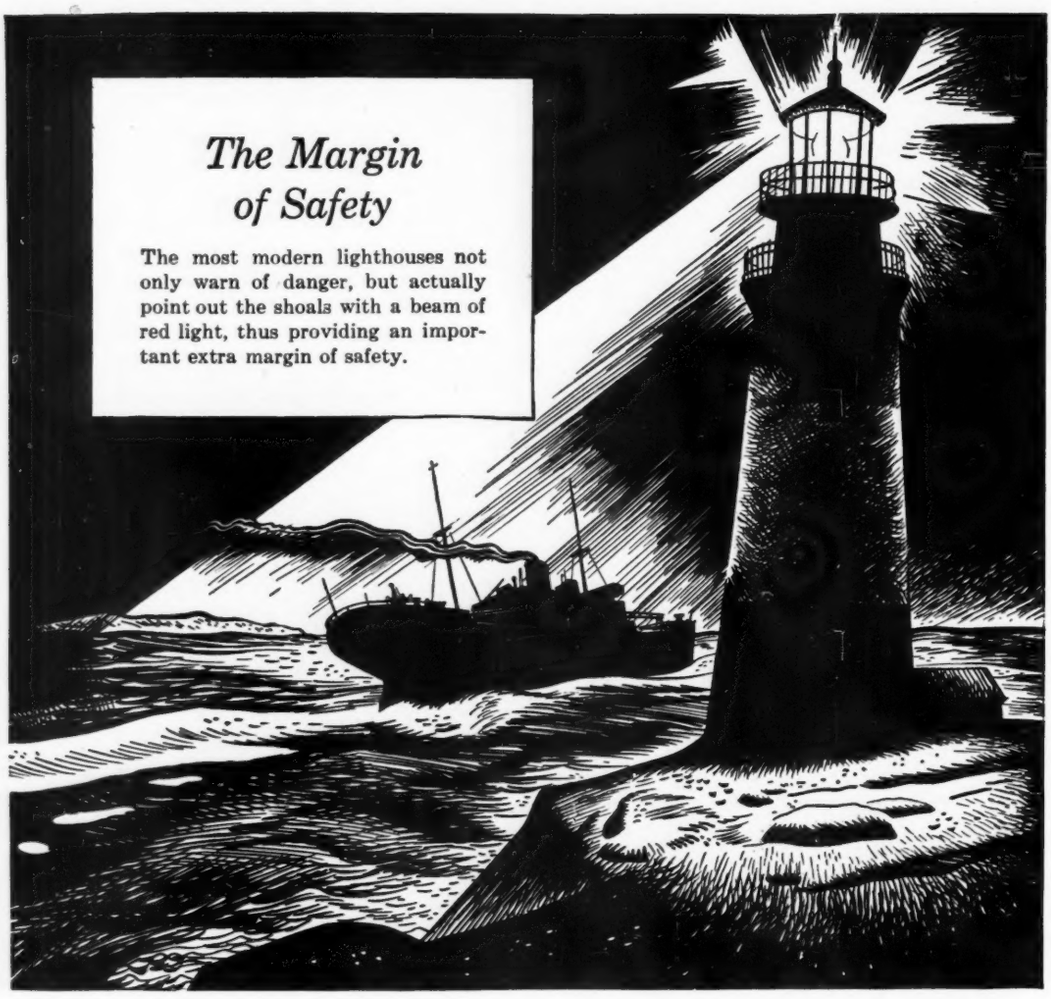

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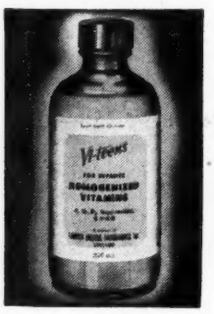

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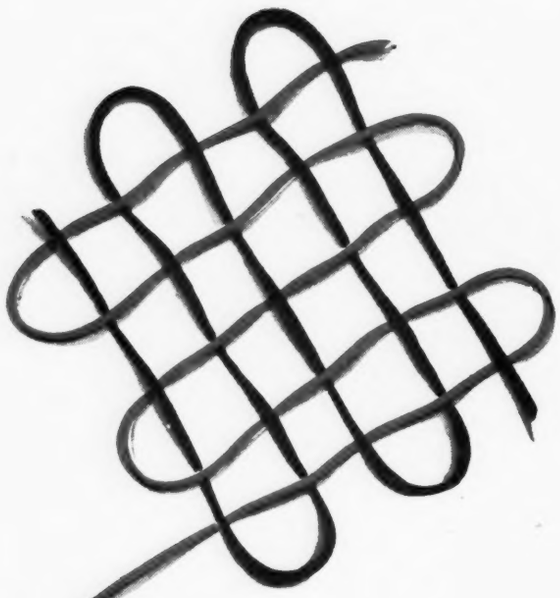

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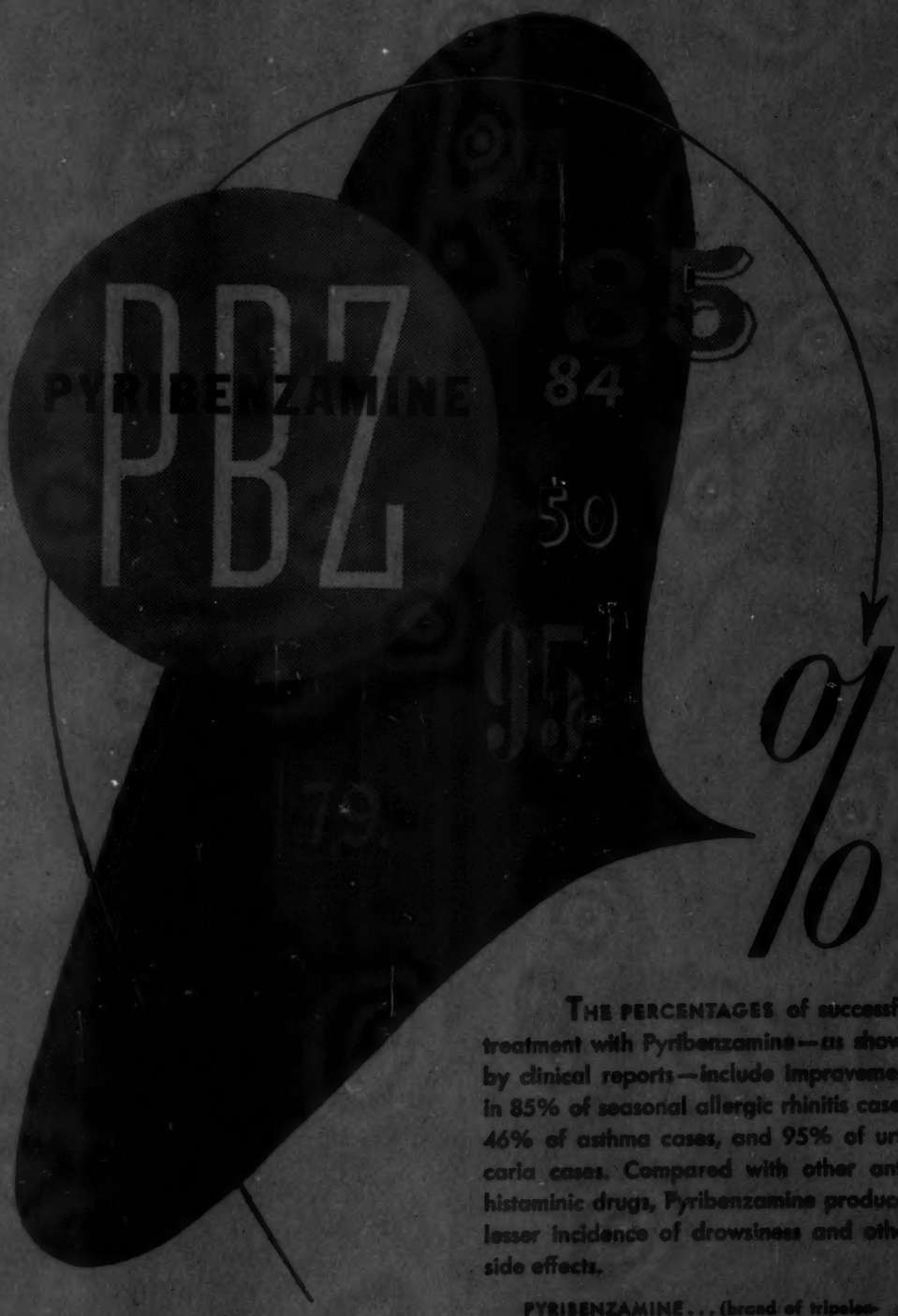

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